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Conversion of vicinal diols into olefins and the synthesis of a semisynthetic analogue of compactin.

by

Philip L. Wickens

A thesis submitted to the faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

DEPARTMENT OF CHEMISTRY

Edmonton, Alberta

Fall, 1995

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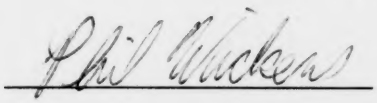

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Dr. D. L. J. Clive

Dr. W. A. Ayer

Dr. R. S. Brown

Dr. M. Palcic

Dr. P. Sporns

Dr. R. H. Mitchell

(External Examiner)

To my family and friends

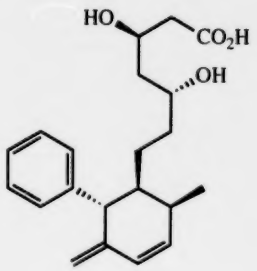
ABSTRACT

The first part of this thesis describes the conversion of *cis*-vicinal dimethanesulfonates into olefins using Te^{2-}, Se^{2-}, arylselenides, and aryltellurides, and the second part describes the synthesis of a semisynthetic analogue of compactin.

The conversion of *cis*-dimethanesulfonates into olefins is useful in making derivatives of 2',3'-didehydro-2',3'-dideoxynucleosides, substances that are considered useful in the treatment of HIV infection.

Reactions of *cis*-vicinal dimesylates with a variety of chalcogenide reagents were explored. Various reducing agents including the use of electrochemistry were studied for the reduction of tellurium and selenium reagents. Initial studies of polymer-supported tellurium reagents were also performed. These studies led to an efficient procedure in which a *cis*-vicinal diol is converted into its dimesylate and then by treatment with Te^{2-}, into the corresponding olefin. The reaction was applied especially in the nucleoside series.

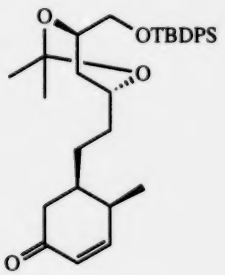
The semisynthetic analogue of compactin we chose to synthesize is compound **A**. Compactin was degraded by a



A

Scheme A

procedure previously developed in this laboratory into the enone **B**, which was then elaborated into **A**. The key feature of the synthesis of **A** is the introduction of the phenyl group stereoselectively.



B

Scheme B

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I would like to express my gratitude to Dr. D. L. J. Clive for his advice and constant encouragement during the course of my graduate studies, and for his assistance in the preparation of this thesis.

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LIST OF ABBREVIATIONS

acac.....acetylacetonate

Bn.....benzyl

t-Bu.....*tert*-butyl

m-CPBA.....*m*-chloroperoxybenzoic acid

DIBAL.....diisobutylaluminum hydride

DMAP.....4-(dimethylamino)pyridine

DMF.....dimethylformamide

DMSO.....dimethyl sulfoxide

HMPA.....hexamethylphosphoric triamide

LAH.....lithium aluminum hydride

LDA.....lithium diisopropylamide

NMO.....4-methylmorpholine N-oxide

PCC.....pyridinium chlorochromate

Ph.....phenyl

PPTS.....pyridinium *p*-toluenesulfonate

Super-Hydride....lithium triethylborohydride

TBAF.....tetrabutylammonium fluoride

TBDMS.....*tert*-butyldimethylsilyl

TBDPS.....*tert*-butyldiphenylsilyl

TCDI.....thiocarbonyldiimidazole

TES.....triethylsilyl

THF.....tetrahydrofuran

TMS.....trimethylsilyl

TPAP.....tetrapropylammonium perruthenate

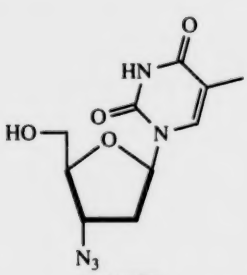
$TsOH \bullet H_2O$.....*p*-toluenesulfonic acid monohydrate

PART I

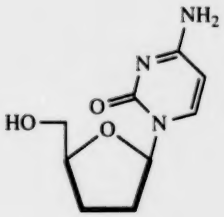
SYNTHESIS OF 2',3'-DIDEHYDRO-2',3'-DIDEOXYNUCLEOSIDES

The Importance of Deoxygenated Nucleosides

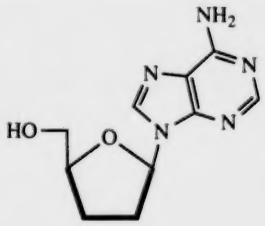
2',3'-Dideoxygenated nucleosides are currently considered useful in the treatment of HIV infection,[1] and several such compounds have received FDA approval[2] for use in appropriate circumstances. These compounds (Scheme 1) are AZT (**1**), ddC (**2**), ddI (**4**), and d4T (**5**). AZT (**1**) has long been used clinically. DDI is prepared from ddA by enzymatic



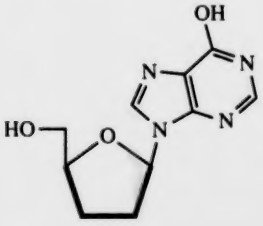
1 (AZT)
3'- azido-3'- deoxythymidine
FDA approved



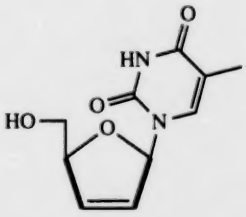
2 (ddC)
2',3'- dideoxycytidine
FDA approved



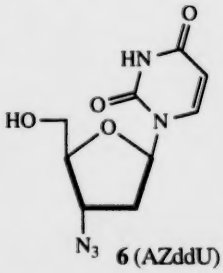
3 (ddA)
2',3'- dideoxyadenosine



4 (ddI)
2',3'- dideoxyinosine
FDA approved



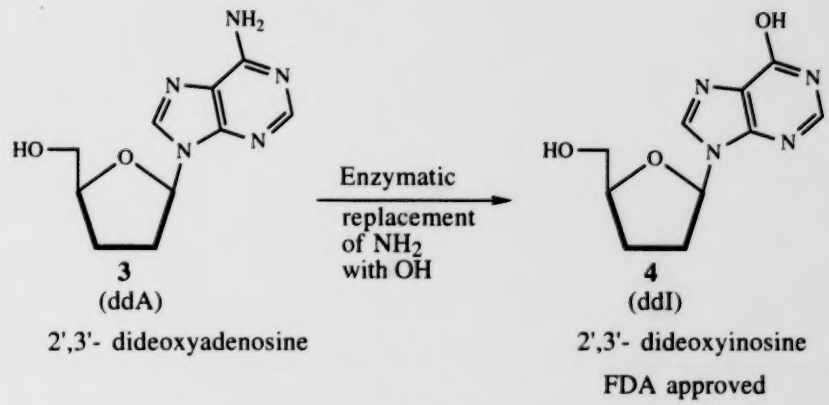
5 (d4T)
2',3'- didehydro-3'- deoxythymidine
FDA approved



6 (AZddU)
3'- azido-3'- deoxyuridine

Scheme 1

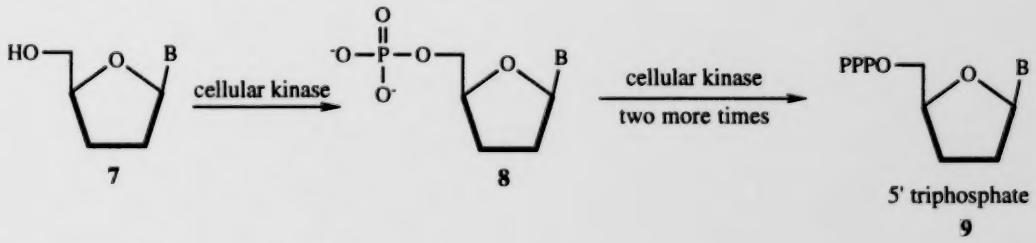
replacement of the NH_2 group by an OH group (Scheme 2).[3]



Scheme 2

Another compound, AzddU (**6**) has gone through at least preliminary clinical trials.[4]

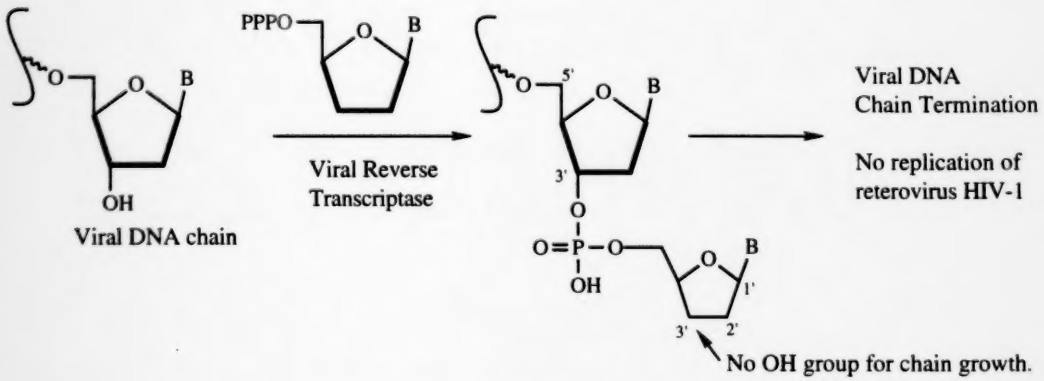
The exact mechanism of action of these drugs is not yet fully understood. Generally, the dideoxynucleosides **7** are pro-drugs and are sequentially phosphorylated by cellular enzymes (kinases) to the 5'-triphosphate **9** (Scheme 3).



Scheme 3

The phosphorylation process can differ in efficiency for different substrates and this possibility can account for some of the differences in activity of the different triphosphate derivatives.

The deoxynucleosides, after *in vivo* phosphorylation, destroy the ability of the retrovirus HIV-1 to replicate, as shown in Scheme 4. In the normal course of events, replication of HIV involves elongation of a growing DNA chain in the 5'→3' direction. Consequently, a nucleoside lacking a C-3' hydroxyl but still accepted by the viral reverse transcriptase (a DNA polymerase) will be attached *via* its phosphorylated C-5' hydroxyl, to the growing DNA chain. This



Scheme 4

process will itself terminate the chain because the product of coupling lacks the requisite functionality at C-3' of the new terminus to permit further chain growth. The dideoxynucleoside triphosphate **9** (Scheme 3), or possibly the terminated oligonucleotide, may also act as a competitive inhibitor of the HIV reverse transcriptase.[5] The biochemical pathways which take place for each dideoxynucleoside are complicated and are being studied in a number of laboratories.[6]

There are, of course, side effects associated with these drugs and they are thought to occur from the fact that the triphosphate **9** as well as the mono and diphosphate, have affinity for other cellular enzymes.[5] The bone marrow toxicity observed in AIDS patients receiving nucleoside treatment is thought to occur because of the inhibition of thymidilate kinase which is a cellular enzyme. The peripheral neuropathy reported in patients being treated with ddC and ddI may be due to inhibition of mitochondrial DNA polymerases.[6]

A strategy that has been followed in recent years for development of anti AIDS drugs is to seek dideoxynucleosides or analogues which are substrates of cellular kinases, and which are triphosphorylated, and are capable of binding to the HIV reverse transcriptase but not to the host enzymes. Multidrug treatments have also been proposed, due to reports of AZT resistance.[7] Recent developments in the synthesis of anti-HIV dideoxynucleosides have primarily focused on modification of the carbohydrate portion of these molecules, since the cellular kinases are more tolerant of these changes than to alterations in the base moiety.[5]

How Dideoxynucleosides are Currently Made

Synthesis of dideoxynucleosides has been studied extensively due to its medical importance. The most attractive approach is to its a ribonucleoside-based route due to the commercial availability of the starting

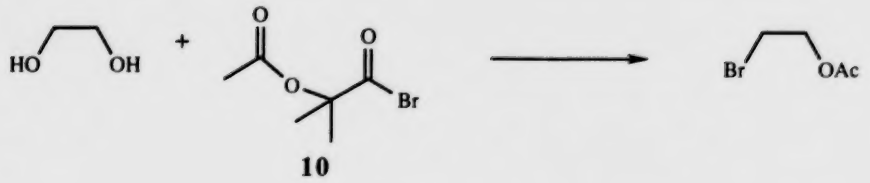
ribonucleosides. These are relatively inexpensive compared to their 2'-deoxy counterparts. Preparation of dideoxynucleosides and the didehydrodideoxynucleosides has been reviewed[5] in 1992 and so only a brief summary is given here. Dideoxynucleosides and analogues can also be made by *de novo* synthesis; this subject has also been reviewed[5] and will not be discussed here.

Dideoxynucleosides (Including Unsaturated Nucleosides) From Ribonucleosides

A clearly attractive approach involves starting with 5'-protected nucleosides, and then using some type of deoxygenation to convert the 2',3'-diol substructure into a double bond. The major methods used in the nucleoside area for converting a 1,2-diol into an olefin are: the Mattocks reaction, the Corey-Winter reaction, the Eastwood olefination, Barton deoxygenation, and the classical Tipson-Cohen method.

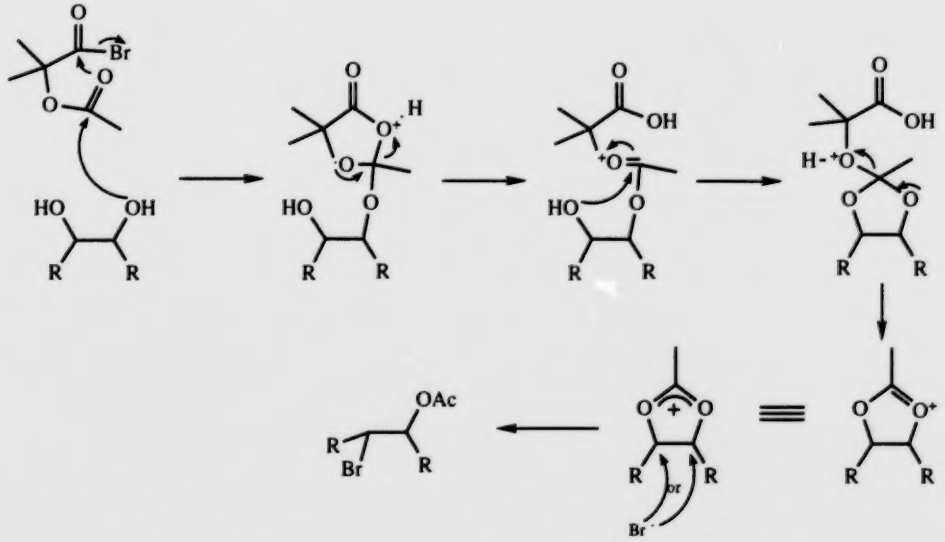
Mattocks Reaction

The Mattocks reaction[8] involves treating vicinal diols with α-acetoxyisobutyroyl bromide (**10**) to form the bromo acetate, as shown in Scheme 5.[9]



Scheme 5

The mechanism of this reaction is summarized in Scheme 6.[10]

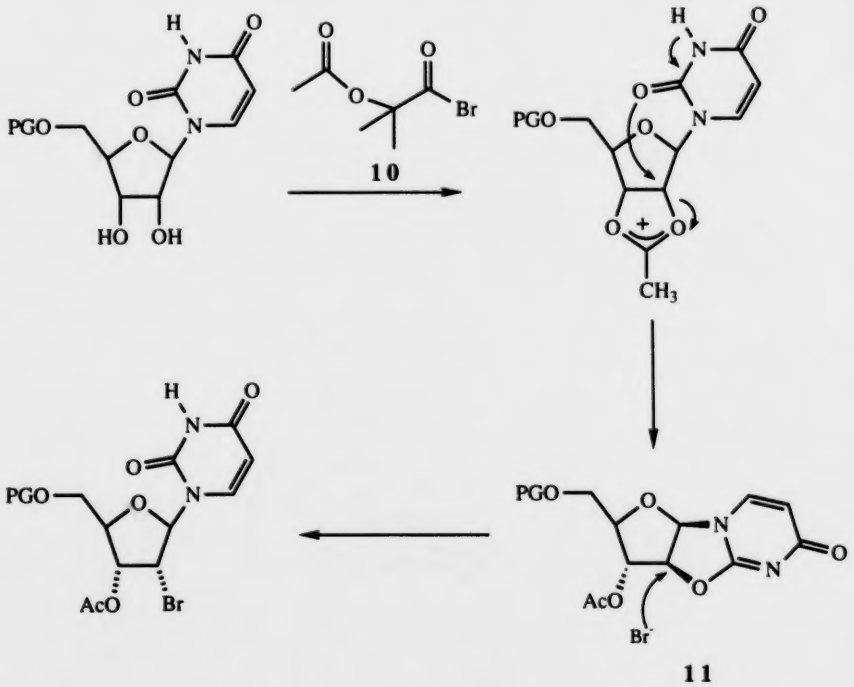


Scheme 6

Reductive elimination of the resulting bromo acetate gives 2',3'-didehydro-2',3'-dideoxynucleosides. The reductive elimination has been done using various methods,[9] of which a zinc/copper protocol appears to be the most versatile, and this procedure has been used to synthesize ddA,[11] ddC,[12] ddG,[13] and ddI.[13] The unsaturated nucleosides can be converted to dideoxynucleosides by catalytic hydrogenation over Pd-carbon[9] or Raney Ni.[9] Direct conversion of the bromo

acetate into the dideoxynucleoside by catalytic hydrogenation utilizing aqueous acetonitrile as solvent and a mixture of NaOAc and Na_2CO_3 as base has also been performed.[14]

A reaction similar to the Mattocks process, but using acetyl bromide, has served in the synthesis of d4T.[15] The Mattocks reaction of uridine analogues is not only regiospecific but it is also stereospecific. The reason for regio- and stereospecificity is understandable in terms of the mechanism summarized by Scheme 7.



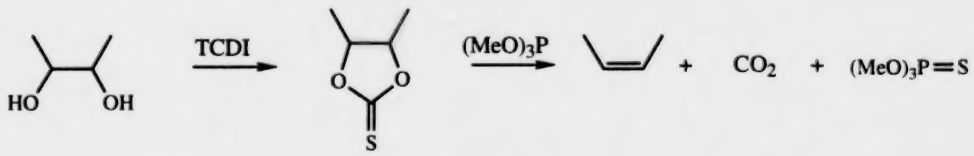
Scheme 7

With other nucleosides such as *N*-acetyl cytidine, or purine nucleosides, bromo acetate formation is not usually regiospecific because these compound types do not form

intermediates corresponding to **11** (Scheme 7). The Mattocks reaction is an attractive approach, although the cost of the reagents is high.

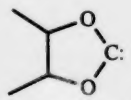
Corey-Winter Reaction

The Corey-Winter reaction[16] involves treating a vicinal diol with thiocarbonyldiimidazole (TCDI) to obtain a cyclic thiocarbonate (Scheme 8) which is then transformed into an olefin by desulfurization-decarboxylation. This reaction



Scheme 8

was devised from the hypothesis that a carbene, of the type shown in Scheme 9, might be unstable and should collapse to carbon dioxide and the olefin. The second reagent was chosen



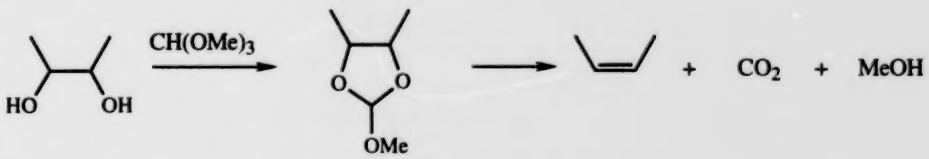
Scheme 9

due to its effectiveness in removing sulfur from organic compounds. Trimethyl- and triethyl phosphite have proved to be effective, although when trimethyl phosphite was used in the synthesis of ddU, extensive *N*-methylation of the base moiety was observed.[17] This problem can be circumvented by

careful exclusion of oxygen or by using 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine[18,19] or triethyl phosphite instead of trimethyl phosphite. DDA, ddG, and ddT have been made using the Corey-Winter procedure with either triethyl phosphite or 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine,[19] although the yields are sometimes low[19] and TCDI is fairly expensive.[20]

Eastwood Olefination

The Eastwood olefination[21] involves treating a vicinal diol with methyl or ethyl orthoformate to produce a cyclic orthoformate (Scheme 10), which then collapses thermally to the olefin.



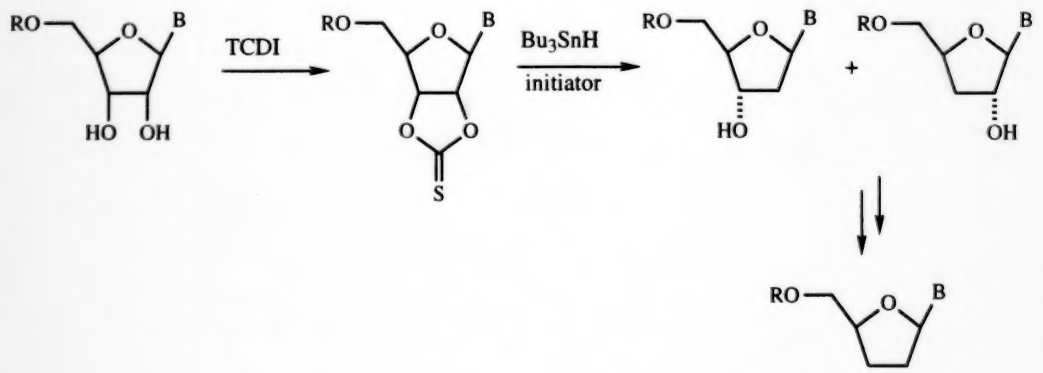
Scheme 10

This procedure did not work for the nucleosides tried until introduction of Ando's modification,[20] which involved using acetic anhydride as the solvent. This allowed formation of ddU from the cyclic orthoformate.[22] Attempts to make ddC and ddA by this procedure failed due to cleavage of the *N*-glycosyl bond.[22] D4T was made using a modification[23] that entailed addition of hydrous zirconium oxide as a catalyst and tributylamine as stabilizer. This procedure for

producing dideoxynucleosides is not attractive due to low yields.

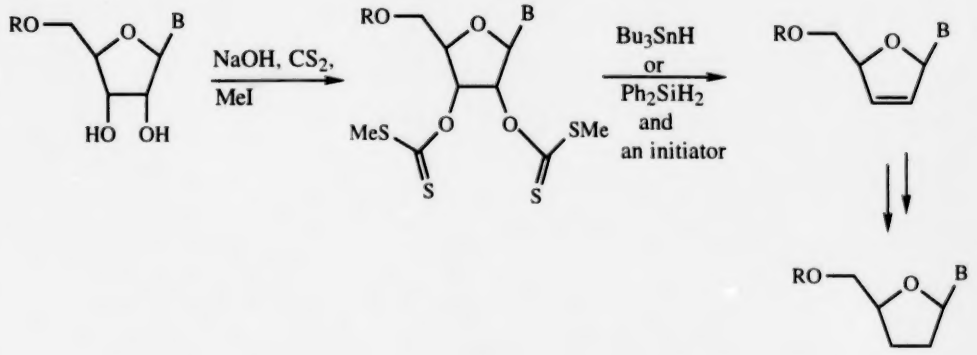
Barton Deoxygenation

The Barton deoxygenation[24] offers two procedures for converting ribonucleosides into dideoxynucleosides. The first involves treating a vicinal diol with thiocarbonyldiimidazole (TCDI) to make a cyclic thionocarbonate (Scheme 11), which is then treated with tributyltin



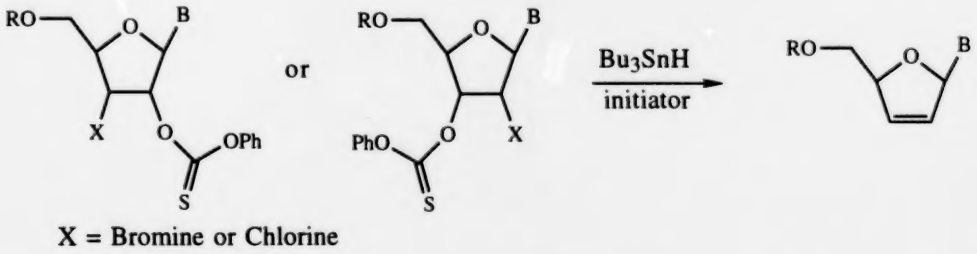
Scheme 11

hydride. A mixture of deoxygenated products is obtained which is subjected again to the same deoxygenation procedure,[25] to afford the dideoxygenated product. The second deoxygenation method is more versatile; it involves treatment of a vicinal diol with sodium hydroxide, carbon disulfide, and methyl iodide to form the bisxanthate (Scheme 12). Treatment with tributyltin hydride then affords the 2',3'-didehydro-2',3'-dideoxynucleoside in high yield.[19]



Scheme 12

Similar conversions of 2',3'-dichloronucleosides to 2',3'-didehydro-2',3'-dideoxynucleosides occur under radical conditions.[26] Various 2' (or 3') chloro (or bromo), 3' (or 2') [(phenoxythiocarbonyl)oxy]nucleoside starting materials (Scheme 13) have also been reported to undergo similar reactions.[27]



X = Bromine or Chlorine

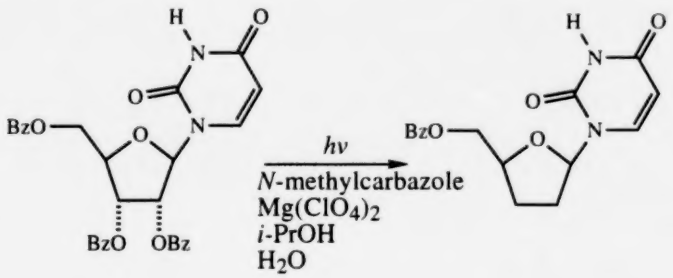
Scheme 13

The Barton deoxygenation is convenient and widely used, although contamination of the final product by tin reagents is sometimes mentioned as a problem. Diphenylsilane has been

substituted for the toxic tributyltin hydride and has been applied to the synthesis of ddA and ddU.[28]

Other Methods

Other methods for making 2',3'-dideoxynucleosides from ribonucleosides are as follows. The uridine derivative shown



Scheme 14

in Scheme 14 was converted to its 2',3'-dideoxy derivative by a photosensitized electron-transfer reaction.[29] This method was also used for the synthesis of purine 3'-azido-2',3'-dideoxynucleosides.[30]

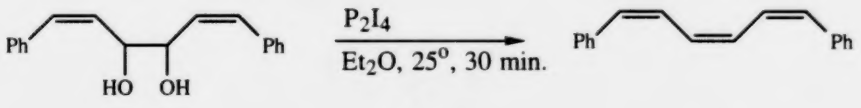
Sodium iodide and zinc dust have been employed to reduce a vicinal dimesylate into an olefin[31] in a low yield.

In summary, current routes to dideoxynucleosides are too expensive and "would seem an impossible economic burden in many parts of the world most devastated by AIDS".[32] Against this background, search for a new, cheaper, and high-yielding method was clearly a worthwhile endeavor.

Conversion of Non-nucleoside Diols into Olefins

Numerous methods have been reported for conversion of non-nucleoside diols into olefins.[33] Many of these have been applied to the nucleoside series, but only the procedures mentioned above appear to be useful in that area. The major methods for the conversion of diols to olefins are described in an exhaustive review by Block,[33] but there are several methods for the diol → olefin conversion that, apparently, have not been tried on nucleosides and several of these may well be useful, as discussed below.

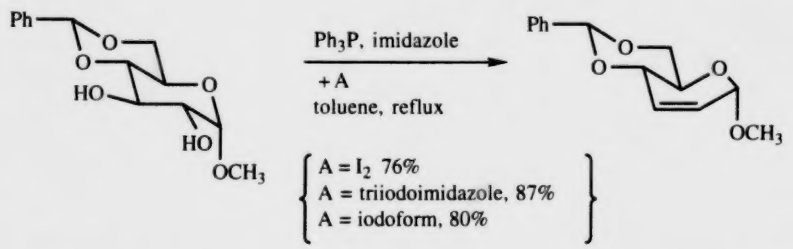
One of these promising methods involves various phosphorus reagents or phosphorus halides. It was discovered in 1928 that vicinal diols could be deoxygenated in a single step simply by stirring at room temperature with an ether solution of diphosphorus tetraiodide (Scheme 15).[34] This



Scheme 15

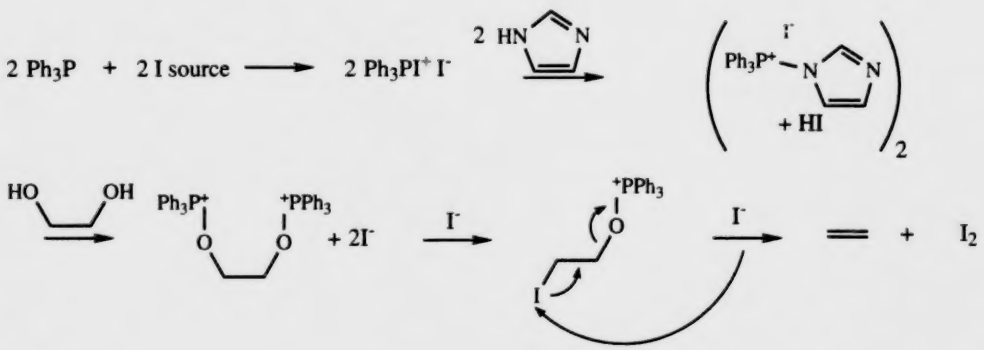
reaction, which is sometimes called the Kuhn-Winterstein reaction, gives variable yields (16-96% on non-nucleoside examples).[35] However, there are a number of mechanistically related procedures involving combinations of phosphines and iodinating reagents.[33] These procedures call for heating the diol in refluxing toluene with a mixture of triphenyl-

phosphine, imidazole, and either iodine,[36] triiodoimidazole,[37] or iodoform[38] (Scheme 16).



Scheme 16

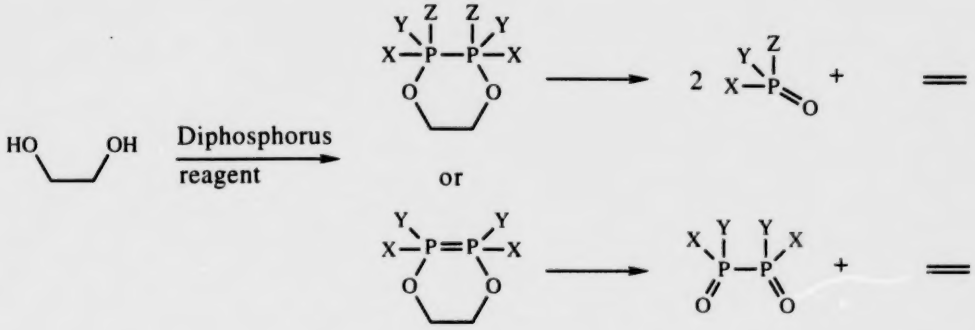
The mechanism is suggested[36] to be that shown in Scheme 17.



Scheme 17

The reagents and conditions seem mild enough to be used in the nucleoside series, and, in fact, a few applications to nucleosides have very recently been reported.[39]

An additional mechanism, which may be possible in the case of P_2I_4, would involve formation of a six-membered ring containing two phosphorus atoms (Scheme 18). The driving



Scheme 18

force to break the six-membered ring would be formation of two strong phosphorus oxygen double bonds at the expense of a phosphorus phosphorus bond.

Background Information Used to Develop Our Strategy for Conversion of Diols into Olefins

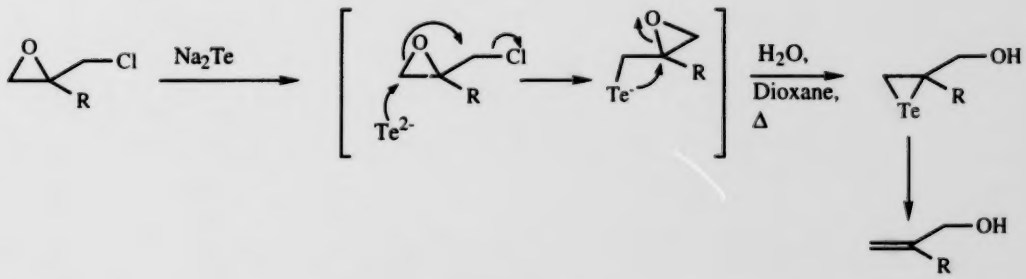
We chose to tackle the conversion of diols into olefins by using attack of a nucleophile on a suitably modified nucleoside substrate. The use of various nucleophilic tellurium and selenium reagents were explored in combination with vicinal diols whose hydroxyl groups had been converted into leaving groups.

Tellurium-Based Reagents

From an obscure branch of organic chemistry, organotellurium chemistry has emerged in recent years as a promising area that has contributed reagents for some important synthetic operations.[40] Tellurium chemistry has

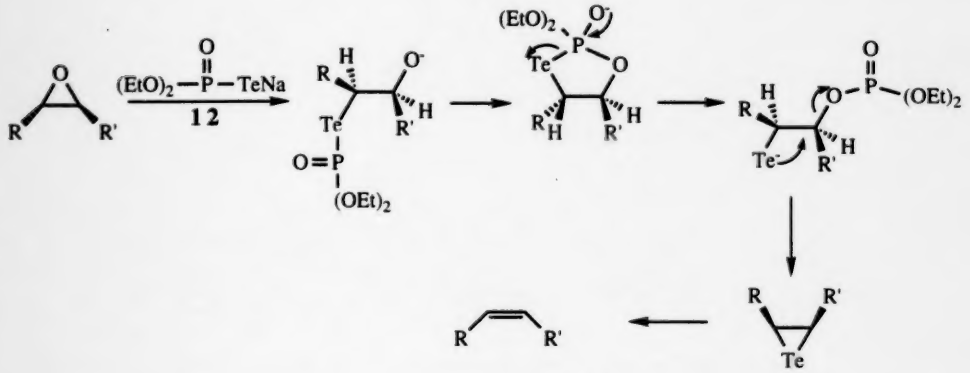
been reviewed many times[40-45] and only those aspects that are relevant to the present work are dealt with here.

Tellurium can be reduced to Te_2^{2-} or Te^{2-} by a number of reducing agents, as discussed later, and these tellurium anions can act as nucleophiles towards various substrates. Epoxides bearing a leaving group in the α-position react with sodium telluride to give allylic alcohols, as shown in Scheme 19,[46] and this process constitutes a useful route to allylic alcohols.



Scheme 19

Another example of a nucleophilic tellurium reagent is shown in Scheme 20.[47] The reagent serves to deoxygenate epoxides to the corresponding olefins.



Scheme 20

The example of Scheme 20, which was developed in this laboratory, and the related work of Scheme 19, provided the basis to our approach for deoxygenating nucleosides. As summarized diagramatically in Scheme 21, a pair of vicinal leaving groups (LG) would be expected to be displaceable by Te^{2-} in such a way as to form an epitelluride, which would spontaneously extrude tellurium, so as to generate a double bond. In order to reduce this idea to practice, a suitable choice of leaving group had to be made.

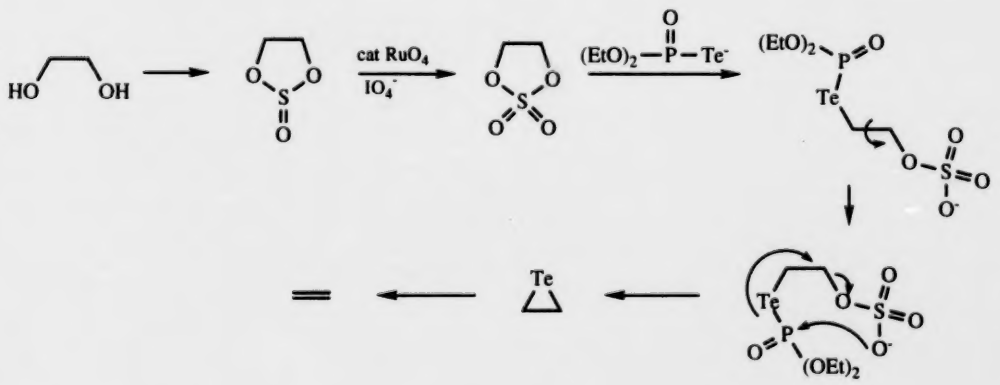
Scheme 21

Cyclic Sulfates and Dimesylates as Substrates

The nature of leaving group was largely dictated by the fact that we were starting with a ribonucleoside, i.e. a vicinal diol. Consequently, the leaving group should be one derivable from a hydroxyl, and it should be of such a type

that the resulting compounds are stable enough for easy handling, and available in good yield.

The obvious choice is a mesylate or a tosylate as these could be used for the exact purpose we had in mind. However, because of the reactivity of epoxides towards tellurium nucleophiles,[47] as seen previously in Scheme 20, we chose to examine cyclic sulfates first. A report by Sharpless[48] had indicated that cyclic sulfates were similar to, but more reactive than, epoxides, and we felt that this property would allow us to extend to cyclic sulfates the reaction that had been developed earlier in our laboratory (Scheme 20) for deoxygenation of epoxides. Thus, we decided to treat a cyclic sulfate with sodium diethylphosphorotelluroate (Scheme 22). Our hope was that the mechanism shown in Scheme 22



Scheme 22

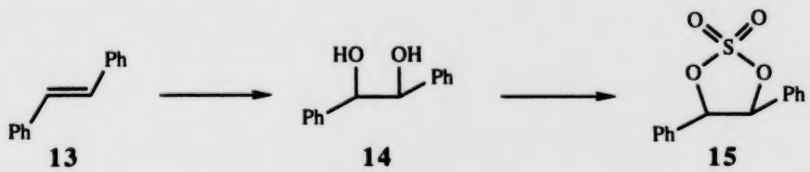
would be followed, so that the starting cyclic sulfate would be converted into an olefin.

DISCUSSION - PART I

Preliminary Investigations

Examination of Cyclic Sulfates as the Substrate and Sodium Diethyl Phosphorotelluroate as the Nucleophile

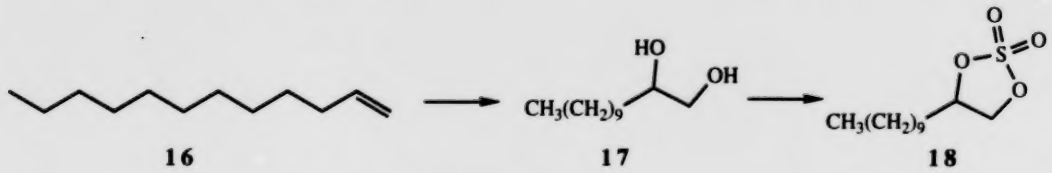
In order to explore the conversion of vicinal diols into olefins in the ribonucleoside series we first examined the use of cyclic sulfates as the substrate and sodium diethyl phosphorotelluroate as the nucleophile. We decided to begin with model compounds, as they would probably be easier to handle. Trans stilbene (**13**) was dihydroxylated[49] to give **14**. The diol was subsequently converted into the cyclic sulfate **15** *via* a method reported by Sharpless[48] (Scheme 23). However,



13 **14** **15**

Scheme 23

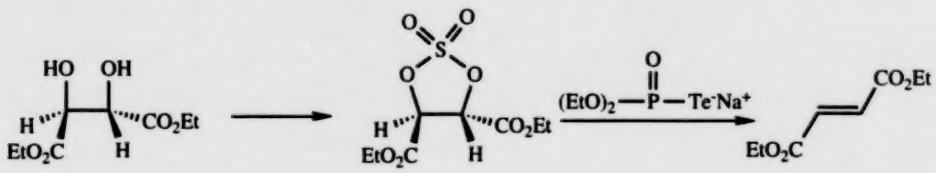
the cyclic sulfate decomposed before we had a chance to use it, and so we decided to try an example based on a straight alkyl chain; such a structure would be more stable (Scheme 24). To this end we dihydroxylated dodecene and converted the diol into its cyclic sulfate.



16 17 18

Scheme 24

Again the sulfate decomposed and so we turned to an example which was already known. Diethyl tartrate (**19**) was converted to its cyclic sulfate[48] **20**, and we found that the compound was stable and could be handled easily. Treatment with sodium diethyl phosphorotelluroate[47] afforded the olefin **21** in 36% yield. We envisage the process to occur by the mechanism shown in Scheme 22. Although this reaction did



19 20 21

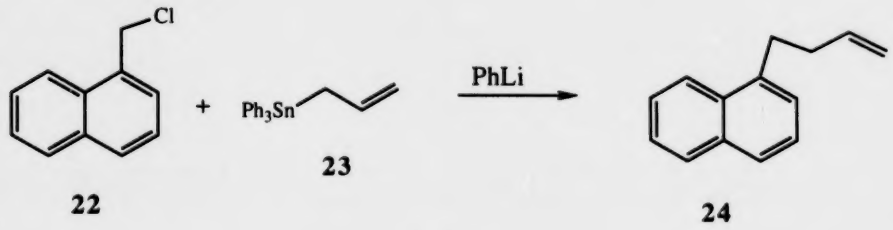
Scheme 25

give us the desired product, the yield was poor, and so we turned our attention to dimesylates, as we thought that these might be more stable – they are certainly used more often as leaving groups.

Use of Dimesylates and the Telluride Dianion

To explore the use of dimesylates we chose a substrate that would have an alkyl chain carrying a terminal diol and

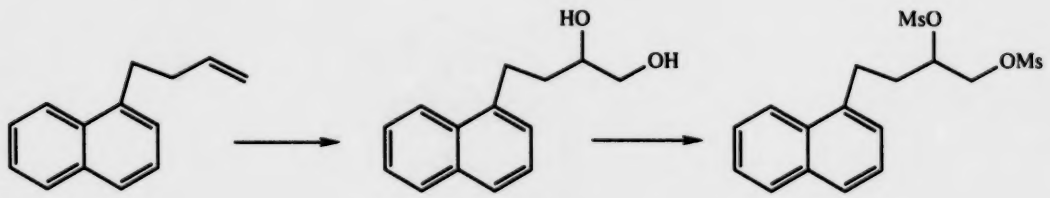
that would also be UV active and nonvolatile. Compound **24** (Scheme 26) satisfied these requirements, and it was made by treating 1-chloromethylnaphthalene **22** with allyl lithium,



22 **23** **24**

Scheme 26

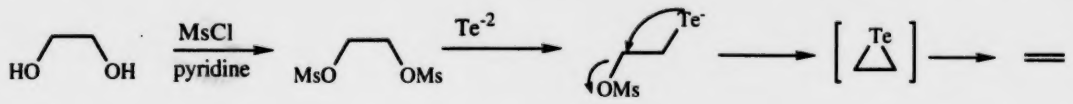
generated *in situ* from allyl triphenyltin (**23**)[50] and phenyllithium. Olefin **24** was dihydroxylated and then mesylated[51] to afford **26** (Scheme 27). We chose to use



24 **25** **26**

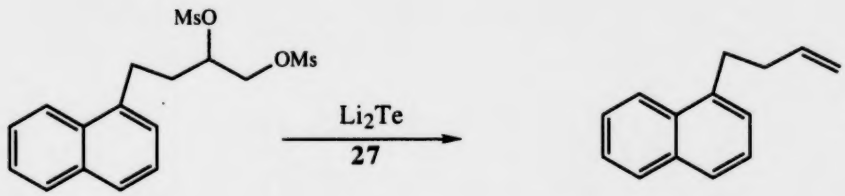
Scheme 27

tellurium dianion[52] as the nucleophile since there was some precedent for tellurium being a strong enough nucleophile to displace tosylates.[53] The reaction process we proposed is shown in Scheme 28.



Scheme 28

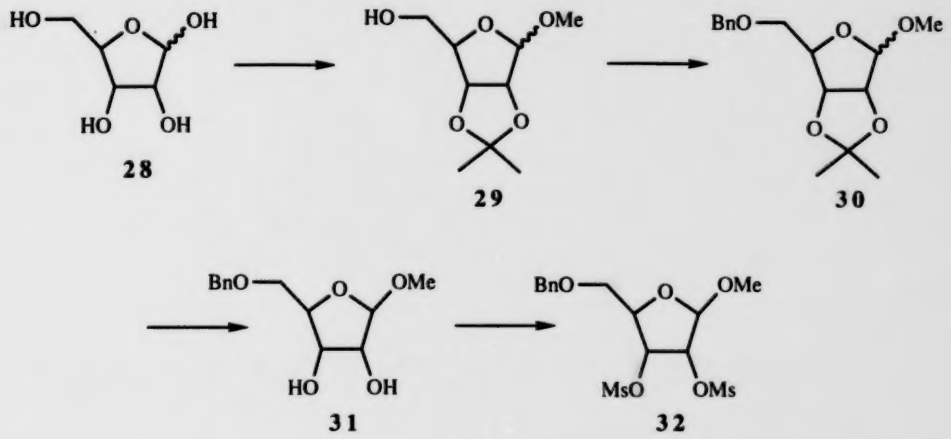
Tellurium metal was treated with Super-Hydride (Et_3BHLi) to obtain Li_2Te[52] (**27**), which was allowed to react with dimesylate **26**. The desired olefin (**24**) was formed in 88% yield (Scheme 29). This procedure looked very promising and



26 **24**

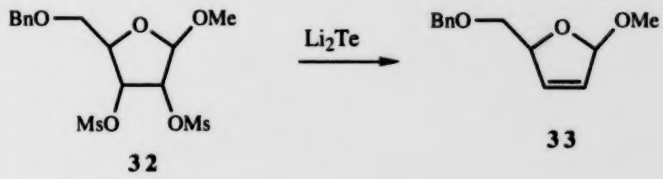
Scheme 29

so we tried it next on a ribose example, which is of course, more closely related to the ribonucleoside series that represents our final target substrates. D-Ribose was converted into the dimesylate **32** (Scheme 30), and treatment



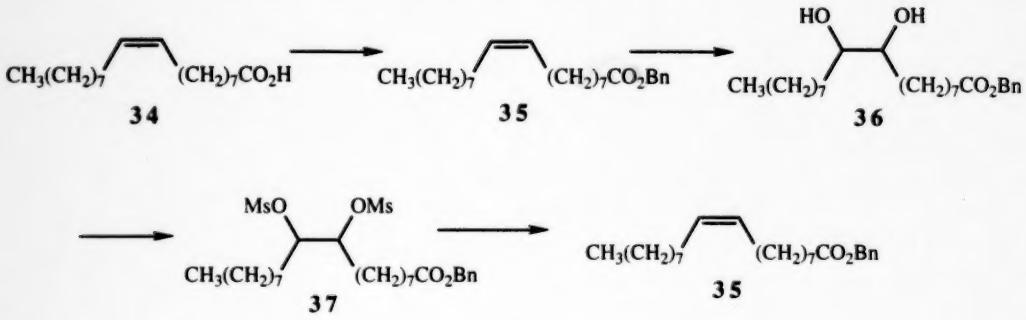
Scheme 30

with Li_2Te, as before, gave the desired olefin in 69% yield (Scheme 31).



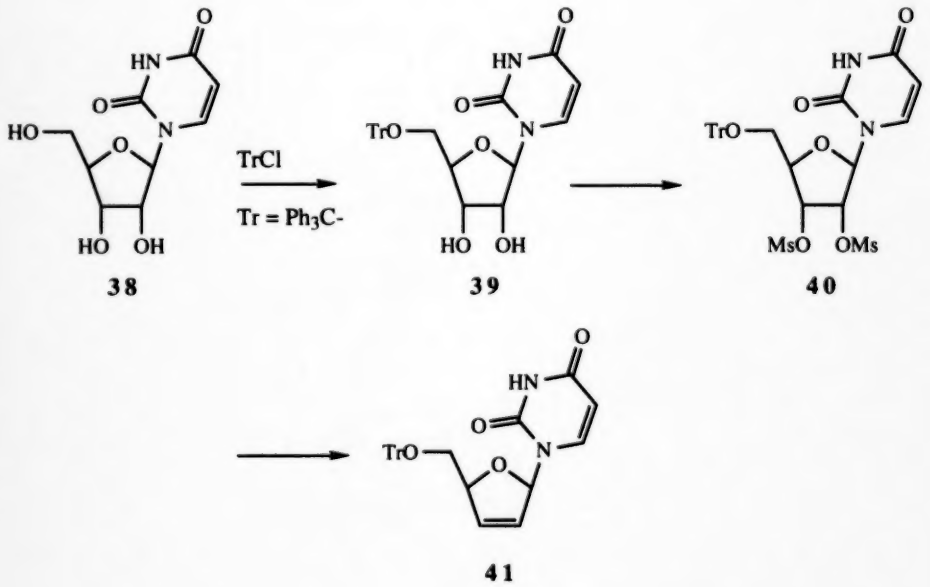
Scheme 31

We then tried another example, in which the mesylates were attached to two secondary carbons. Oleic acid was protected, dihydroxylated, and converted to its dimesylate (**34** → **35** → **36** → **37**). This was converted into the olefin (Scheme 32) in 83% yield, again using Li_2Te.



Scheme 32

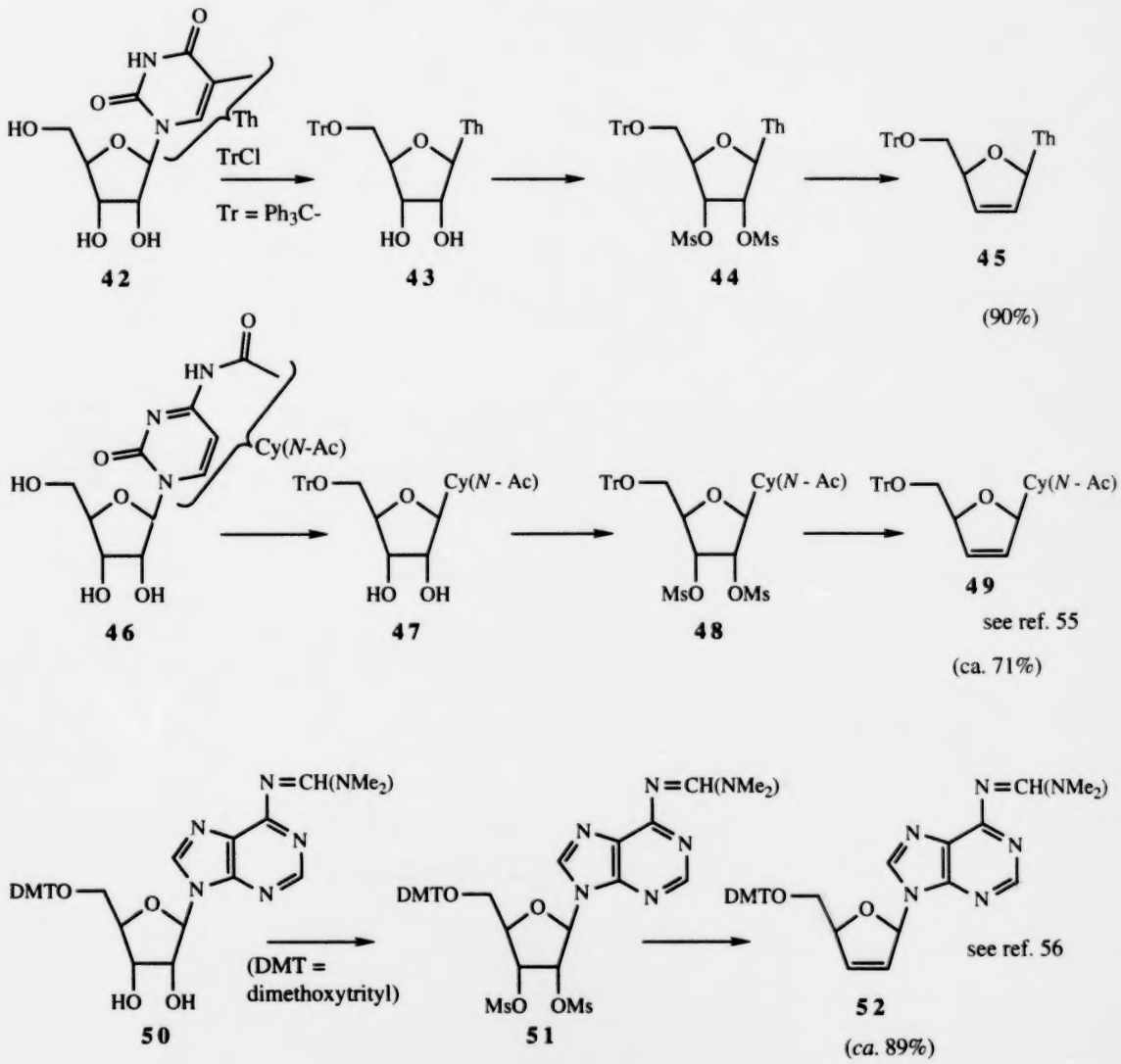
At this point we were confident enough to test the nucleoside series. Uridine (**38**) was protected at C(5')



Scheme 33

by tritylation. The resulting diol **39** was dimesylated, and deoxygenated in 80% yield to the desired 2',3'-didehydro-2',3'-dideoxyribonucleoside (**41**). Various other nucleosides, thymidine (**42**)[54], *N*-acetylcytidine (**46**),[54] and the *N*-protected

5'-protected adenosine **50**,[54] were also tested and the yields in the olefination step are shown in Scheme 34.

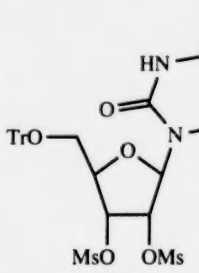


Scheme 34

Our results show that the Li_2Te procedure is useful for the conversion of ribonucleosides into 2',3'-didehydro-2',3'-dideoxynucleosides, but we wanted to determine if dimesylates

can be converted into olefins with other reagents, and we also wished to establish the limitations of our reaction.

Simple vicinal dimesylates have been converted into olefins by the action of sodium naphthalenide[57] or of iodide ion,[58] and so we tested both of these systems, as shown in Scheme 35. A complex mixture was the result in each case, emphasizing the fact that only very mild procedures are useful in the nucleoside series.



40

40 —(Na Naphthalenide)→ Complex Mixture

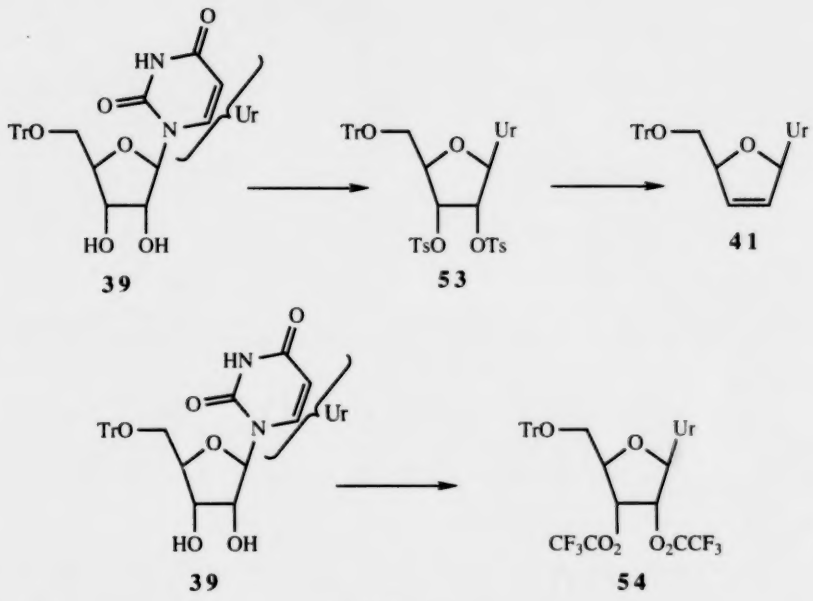
40 —(KI 18-Crown-6; Zn Dust, DMF)→ Complex Mixture

40 —(KI 18-Crown-6; Zn-Cu couple, DMF)→ Complex Mixture

Scheme 35

Limitations of the Li_2Te Reaction

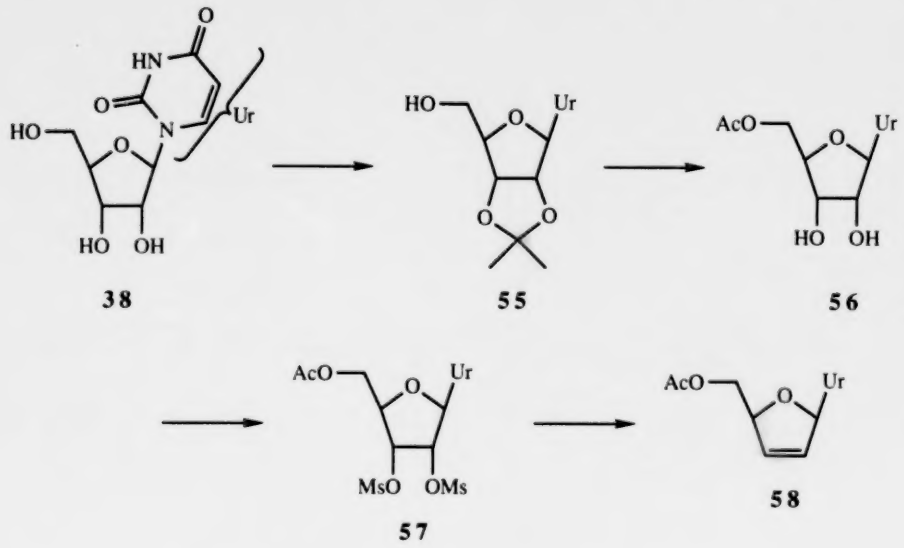
First, we decided to look at the possibility of using ditosylates, or di(trifluoroacetates) as leaving groups (Scheme 36). In the case of **39**, the ditosylate **53** was formed only in 29% yield; the olefination to **41** went in 60% yield,



Scheme 36

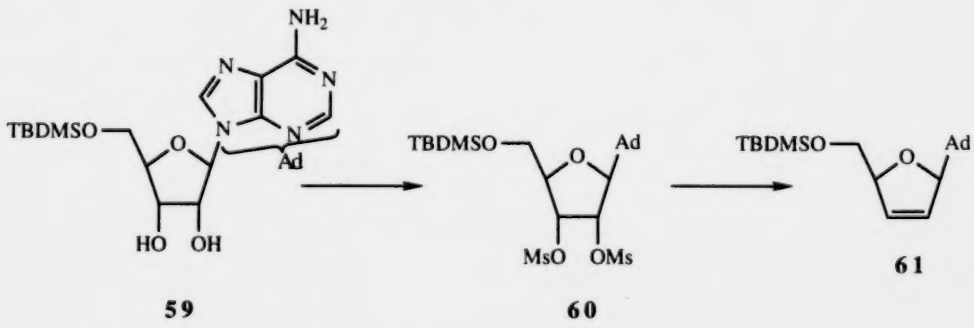
using Li_2Te. Compound **54** could not be made using trifluoroacetic anhydride and pyridine. Neither the tosyl nor the trifluoroacetoxy leaving groups seemed very promising and so it would appear that the choice of leaving group is limited. This, however, is not a serious restriction because the one suitable leaving group is very easy to generate, and we have found no nucleoside example where its use poses a problem.

We then examined some variations in the 5'-hydroxyl protecting group. The 5'-acetyl dimesylate **57** was easily prepared, but its conversion to olefin **58** proceeded in poor yield (14%).



Scheme 37

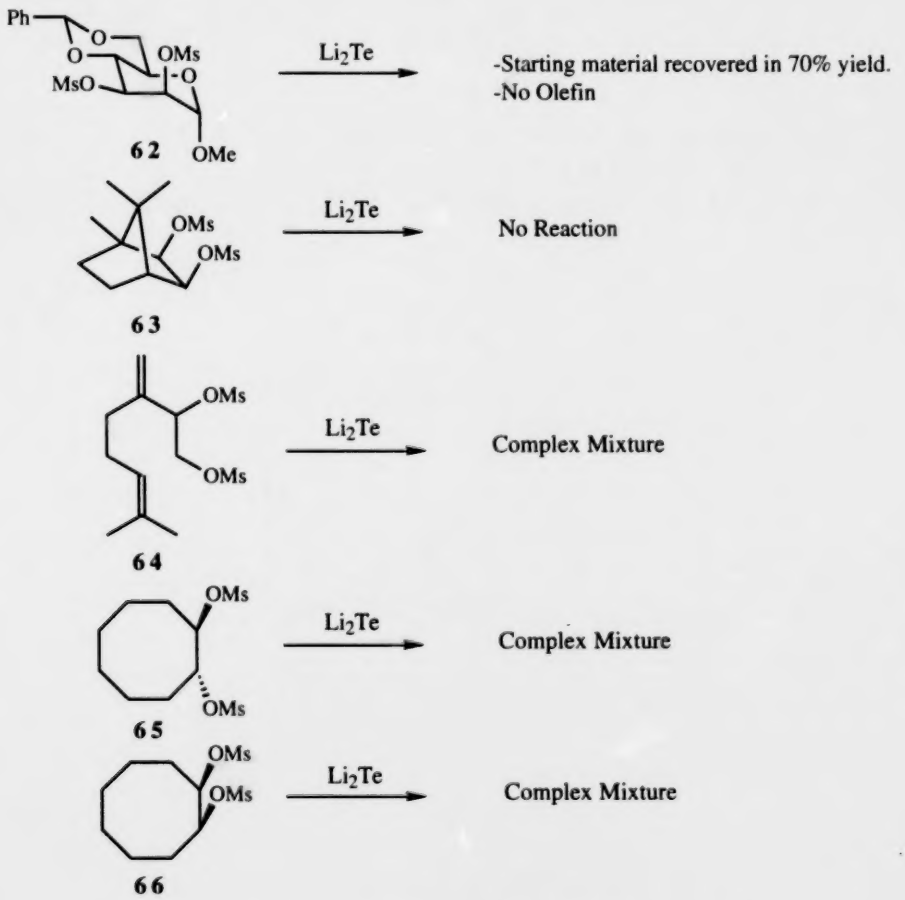
With compound **59**,[54] mesylation gave **60** in 78% yield, and olefination, to produce **61**, was also efficient (78%). This



Scheme 38

last experiment showed that the TBDMS protecting group on the 5'-hydroxyl did not affect either stage of the deoxygenation, and it was also clear that the amino group in the base moiety of adenosine need not be protected.

We then looked at limitations on the nature of the dimesylate. A variety of dimesylates were made and tested by Paulo Scarbi[59] and some of these are listed in Scheme 39. In due course, he will deal with a full analysis of his results, but the main conclusions are that the dimesylate should not be too hindered and that the two mesyloxy groups must be syn coplanar or able to attain such a conformation.

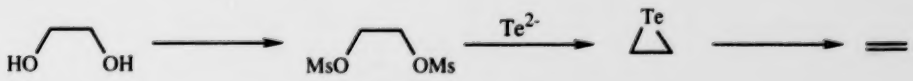


Scheme 39 (Paulo Sgarbi's work)

In summary, mesylates are the best leaving groups for the reaction, the nature of the C(5') hydroxyl protecting group is not critical, and an amino function in the base component need not be protected. With non nucleoside substrates steric factors can become important, and the mesyloxy groups must be in a syn coplanar relationship or be able to adopt such a relationship.

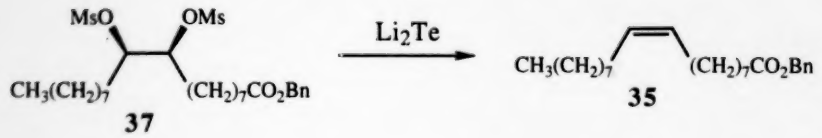
Mechanistic Considerations

Scheme 40 shows a simple diagram of the process which is involved in our reaction without mechanistic detail.

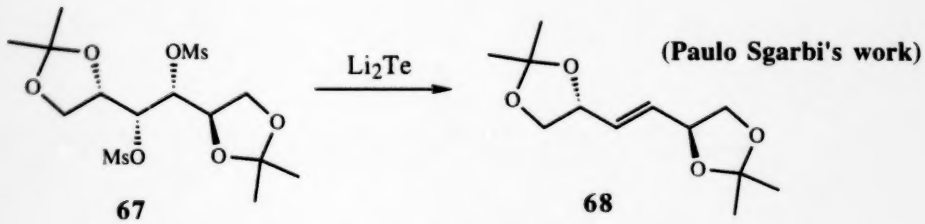


Scheme 40

The results with compounds **37** and **67** (Scheme 41) are consistent with this mechanism, but do not exclude operation of an SET pathway.



37 35



67 68

(Paulo Sgarbi's work)

Scheme 41

In an attempt to intercept possible carbon radical intermediates arising from an SET mechanism, compound **69** was

69 70

Scheme 42 (Paulo Sgarbi's work)

prepared.[59] Under our standard conditions Paulo Sgarbi obtained **70** (whose stereochemistry was established by ^{1}H NMR techniques as described in the next paragraph) in 95% yield and no cyclized product was observed.

The *trans*-stereochemistry of the C(6)-C(7) double bond in **70** was determined from the coupling constant of the hydrogens on the double bond. The coupling constant was 16 Hz which is expected from a molecule with *trans*-stereochemistry. A value of *ca.* 8-10 Hz would be observed if

the stereochemistry was *cis*. The measurement of 16 Hz was obtained by first decoupling the hydrogens on C(5) (CH_2) and C(8) (CH_2) to simplify the spectrum and, because the molecule is symmetrical, the coupling constant was then measured from the proton satelites corresponding to $R^{13}CH=^{12}CHR$. In this situation (ie. one carbon is ^{13}C and the other is ^{12}C) the molecule is unsymmetrical and the coupling can be measured.

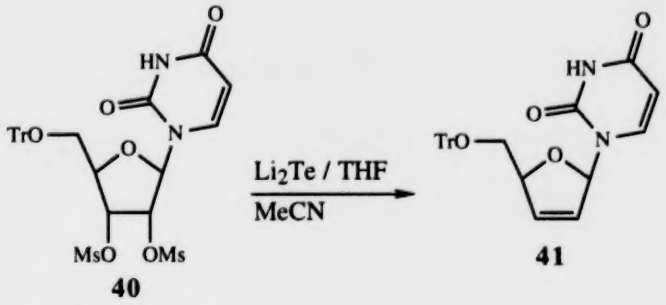
In summary, our proposed nucleophilic displacement mechanism is consistent with the results obtained so far, but other pathways have not been excluded.

Industrial Considerations

We had now established that the reaction of Li_2Te with 2',3'-dimesylates of the nucleoside series constitutes a reliable method for generating the corresponding 2',3'-dideoxy-2',3'-didehydronucleosides. The reaction works for all the examples studied, a range which covers the major types of nucleosides. Our next objective was to make the reaction suitable for industrial use. Costs of the substrate and nucleophile, ease of preparation of both materials, the cost and handling convenience of the solvents and the reducing agent, and whether the tellurium could be used catalytically or recovered, as well the ease of scaling up the reaction were all considerations that had to be examined.

Dimesylates are simple and cheap to prepare.[51] Tellurium metal is also cheap,[60] but the cost of reducing it to Te^{2-} depends on the reducing agent used. We had used THF

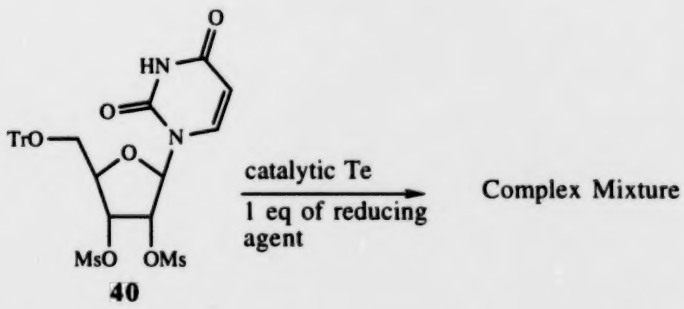
as the reaction solvent but we were informed that acetonitrile was preferable.[61] Accordingly a reaction (shown in Scheme 43) was performed to see if acetonitrile could be used.



Scheme 43

Uridine dimesylate (**40**) was converted into **41** in 99% yield in this experiment, and so it was clear that the reaction could work well in solvents other than THF.

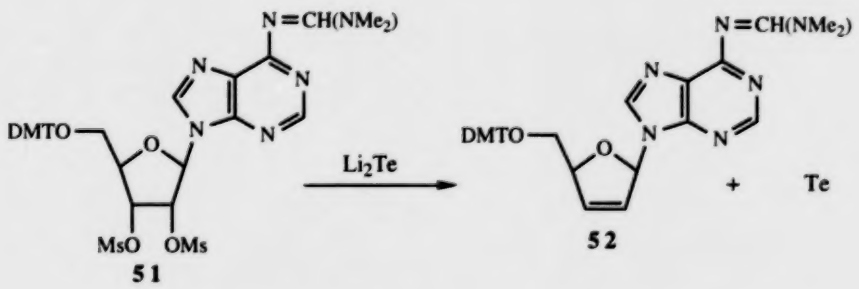
Attempts to run the reaction (Scheme 44) in a manner that is catalytic in tellurium, but using a stoichiometric



Scheme 44

amount of reducing agent, were unsuccessful in the nucleoside series because the starting dimesylates and/or products are sensitive to the reducing agents (Na-Naphthalene, NaH, Super-Hydride).

We also tried an experiment in which we recovered the tellurium, as summarized in Scheme 45. The reaction was run on a small scale (0.128 mmol of dimesylate, 0.269 mmol of tellurium), and 53% of the initial charge (34 mg) of tellurium was recovered.

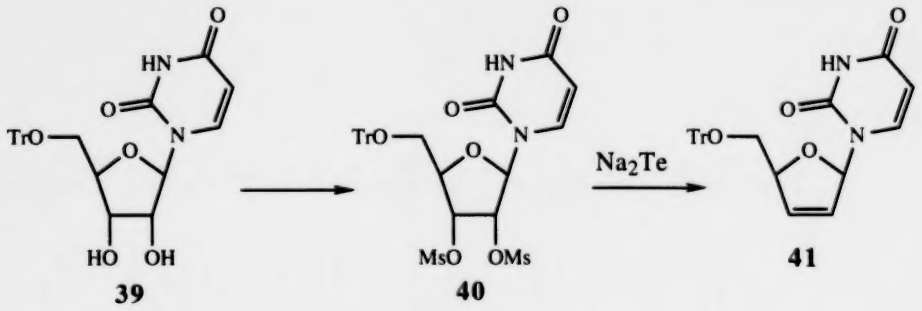


Scheme 45

The tellurium precipitates at the end of the reaction and the mixture was then filtered through a pad of β-cyclodextrin. The tellurium powder was then separated by dissolving the β-cyclodextrin in boiling water and filtering the hot mixture.

We also explored electrochemical methods to reduce tellurium reagents, as this method would avoid the expense of hydride reducing agents, and our experiments in this regard are discussed later.

Most of our work was done on a small scale, but we have also carried out a larger scale run (Scheme 46). The



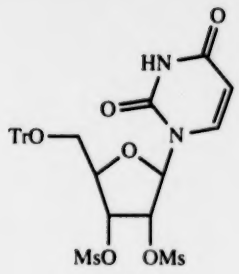
39 40 41

Scheme 46

mesylation to form **40** was performed on a *ca.* 6 g of **39** and the yield was 74%. The olefination was done in acetonitrile, using 2.6 g of **40**, and we were able to isolate the product in 75% yield, as opposed to 80% for a deoxygenation run on 100 mg. We have, however, not optimized the large scale experiment.

Reduction of Tellurium Metal

Many reducing agents were examined to determine if they would be suitable for generation of Te^{2-} as a reagent for reactions with a full range of nucleosides. We evaluated both known and potential ways of generating the telluride dianion, and some of these are listed in Table 1. If there was reduction of tellurium, as seen by a color change, then the substrate **40** (Scheme 47) was added, as indicated in



40

Scheme 47

Table 1 Reduction of Tellurium Metal

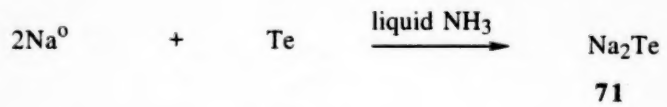
	Metal	Reducing Agent	Usage of 40	Results	Refs
1	Te	Na naphthalenide	Yes	No Olefin	62
2	Te	Rongalite/H_2O	Yes	No Olefin	63-65
3	Te	Rongalite/DMF/ $NaHCO_3$	Yes	No Olefin	
4	Te	$Na_2S_2O_4$	No	No Reduction	66, 67
5	Te	hydrazine/ NaOH	Yes	No Olefin	68
6	Te	hydrazine/LiOH /DMF or THF	No	No Reduction	
7	Te	$NaBH_4$/THF or DMF	Yes	No Olefin	69-71
8	Te	$Bu_4N^+BH_4^-$	Yes	No Olefin	*Cf.* 63
9	Te	$LiBH_4$	No	No Reduction	
10	Te	Red-Al/THF	Yes	6% Yield of Olefin	
11	Te	$LiAlH_4$/THF	No	No Reduction	
12	Te	Et_3BHLi/ addition of acetone	Yes	30% Yield of Olefin	

13	Te	L-Selectride/ THF	Yes	62% Yield of Olefin	
14	Te	DIBAL-H/THF	No	No Reduction	
15	Te	NaH/DMF or dioxane	Yes	No Olefin	72,73
16	Te	LiH/THF	No	No Reduction	
17	Te	$LiH/Et_3B/THF$	No	No Reduction	
18	Se	LiH/THF	No	No Reduction	

the Table 1.

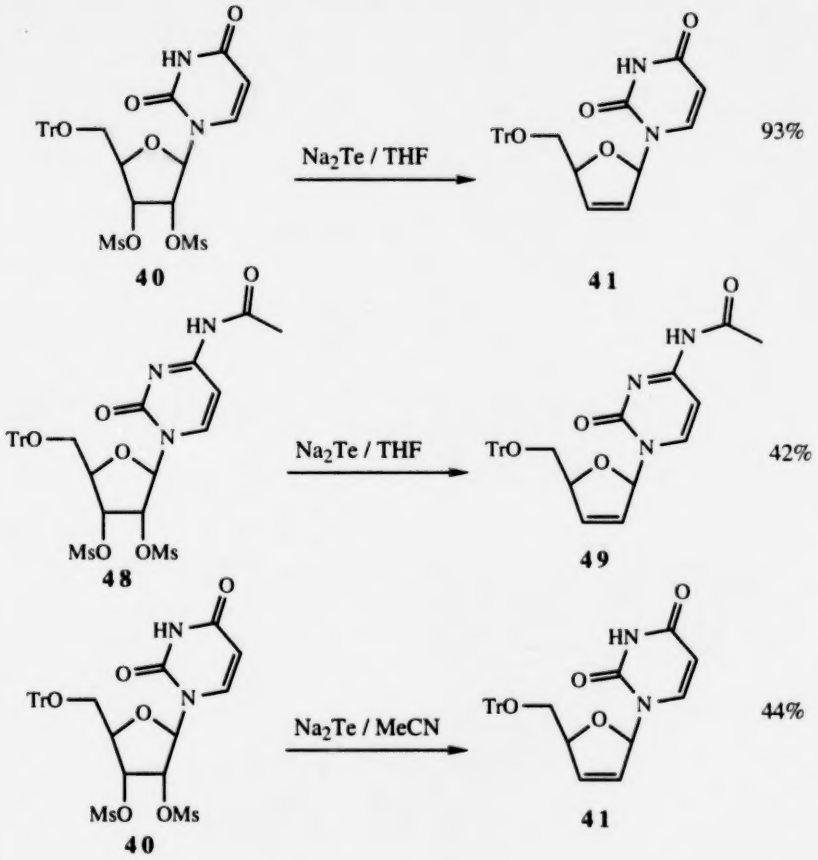
Some of the reducing agents required the presence of water, and we found that complex mixtures were formed when protic solvents were used (Table 1, entry 2). When the reducing agents that required water as a solvent were attempted in THF instead, a purple solution resulted and a complex mixture was formed on addition of nucleoside dimesylates. When Super-Hydride was used as the reducing agent in THF, the solution went from clear to purple and finally changed to a milky white suspension. We formed the impression that most of the reducing agents were not strong enough to form the dianion and other tellurium species[74] were present. We also established that the reducing agent had to be used in near stoichiometric quantities, as an excess of reducing agent damaged the nucleoside dimesylate. We tried running an experiment in which we added excess Super-Hydride for reduction of the tellurium, and we then attempted to quench the excess of reducing agent with a few drops of acetone (Table 1, entry 12). However, the yield fell from

80% to 30%, possibly because of the presence now of a base (the alkoxide derived from isopropanol, itself resulting from reduction of acetone). One potential way to avoid an excess of reducing agent would be to use a polymer support for the tellurium reagent, and this approach is discussed later. In addition to the reducing agents shown in Table 1 we also tried Na in liquid ammonia (Scheme 48).



Scheme 48

Disodium telluride **71** was formed as a whitish-beige powder after evaporation of the ammonia. This method of reduction of tellurium seemed promising, as shown by the first of the results in Scheme 49, and because of the fact that sodium and liquid ammonia are not expensive. However, when the reaction was performed on the *N*-acetylcytidine example, the yield dropped to 42%. When the reaction was

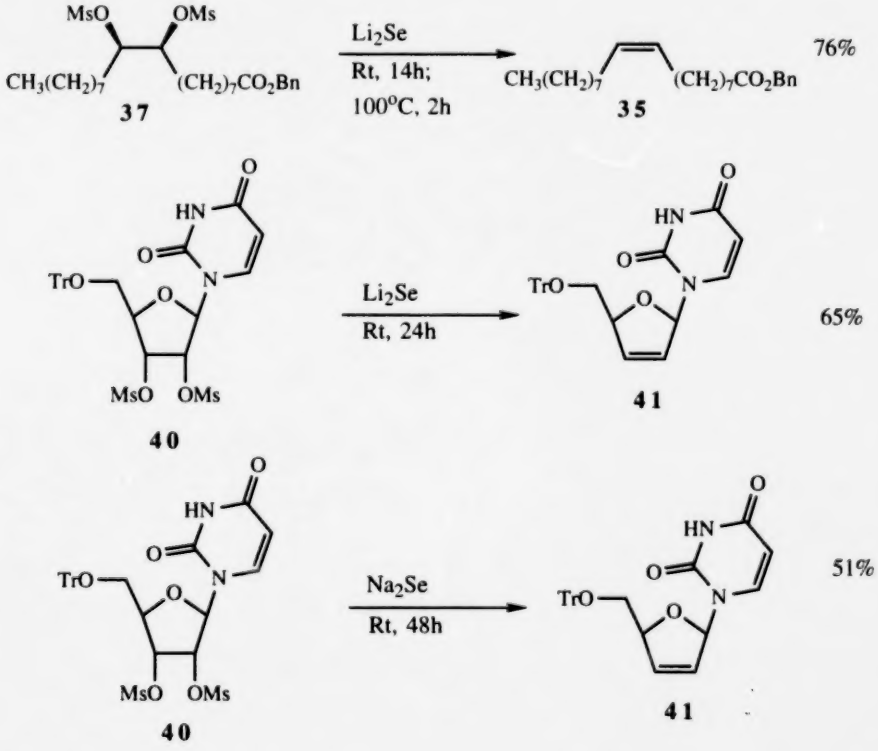


Scheme 49

performed using acetonitrile as the solvent the yield was also low (44%). We recognize that the reagent made from Et_3BHLi may be a boron-complexed species, but such complexation is not essential since Na_2Te also works well in the case of **40** (first reaction in Scheme 49). Additional experiments should be performed to evaluate the scope of the use of Na_2Te, but we have not done this.

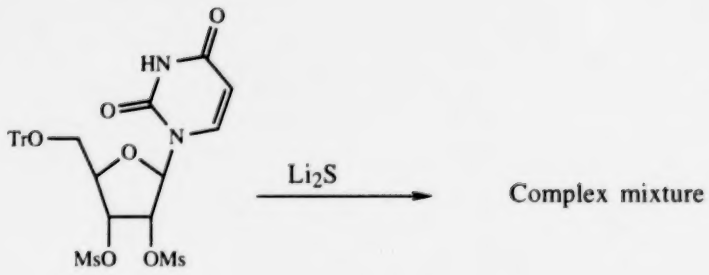
Use of Selenium as a Nucleophile

The use of selenium as a nucleophile was also studied. Treatment of dimesylates **37** and **40** with selenide dianion (from Se and Et_3BHLi[52] or Na/liquid NH_3[68]) does lead to the olefin, but the reaction is slower than in the case of tellurium.



Scheme 50

We also tested the sulfide dianion (S and Et_3BHLi[52]) (Scheme 51) in the hope of generating an episulfide, which could then be desulfurized, but a complex mixture was obtained.

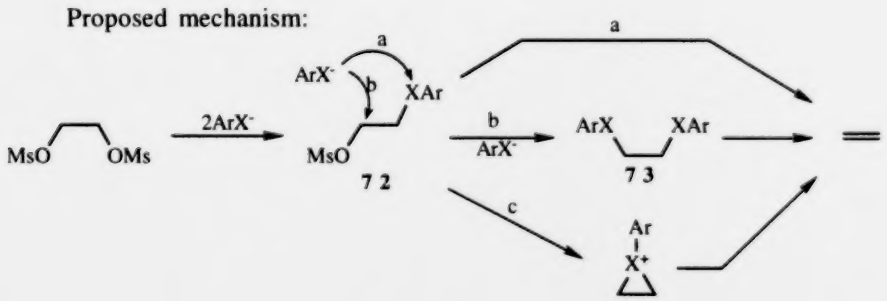


Scheme 51

At this point we turned our attention to the use of aryl tellurides and aryl selenides, as described in the next section.

Use of Aryl Tellurides and Aryl Selenides

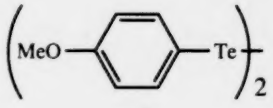
In principle, treatment of 1,2-dimesylates with ArX^- (X = Te or Se), derived from the corresponding ArXXAr, could lead to olefins, as shown in Scheme 52. β-Mesyloxyselenides **72** are known to collapse to olefins[75] but the reported



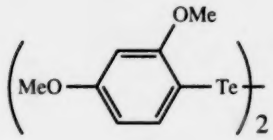
Scheme 52

examples were generated in a totally different manner. 1,2-Di(phenylseleno)ethane **73** (Scheme 52, X = Se) is known to be

unstable[76] with respect to formation of the olefin, at least in the presence of silica gel, and we suspect that corresponding tellurium compounds might show a greater tendency to collapse to olefins. We initially made di(4-methoxyphenyl)ditelluride (**74**)[77] but we found that di(2,4-dimethoxyphenyl)ditelluride (**75**)[78] (Scheme 53) is more stable. Our experiments with $ArTe^-$ are shown in Scheme 54. The

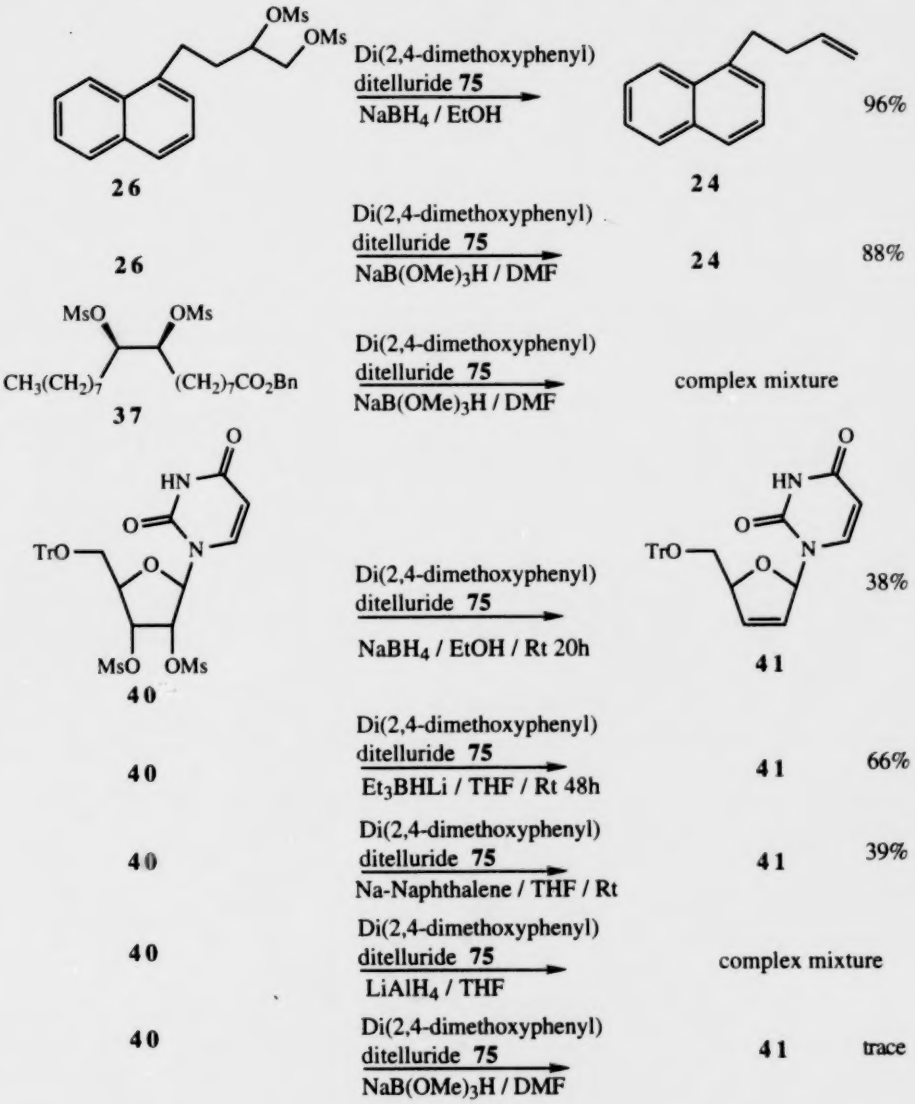


74



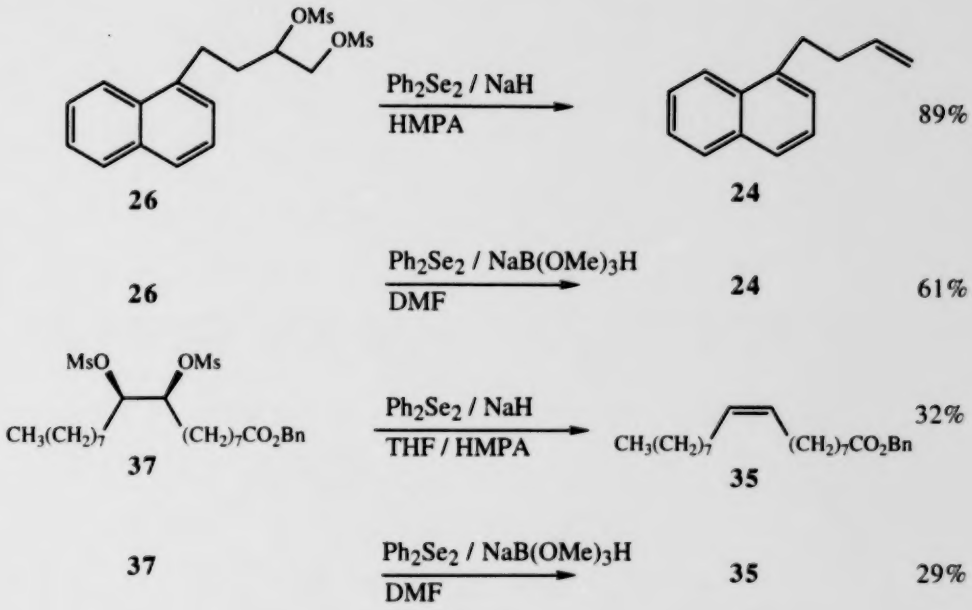
75

Scheme 53



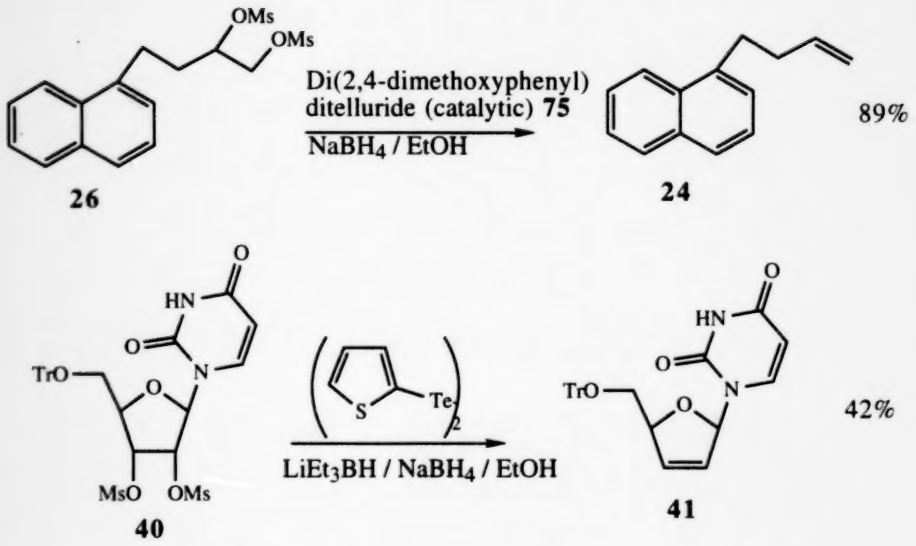
Scheme 54

reaction works well in the case of compound **26**, but when we tried compounds **37** and **40** the result was highly dependent on the reducing agent. We also evaluated diphenyl diselenide, as shown in Scheme 55. The reaction worked well for compound



Scheme 55

26, but again the result seemed to depend on the reducing agent. The phenylselenide anion was not very efficient in converting **37** into the olefin. An experiment with a catalytic amount of ditelluride **75** was performed along with an example in which dithienyl ditelluride[79] was also tried, as summarized in Scheme 56.



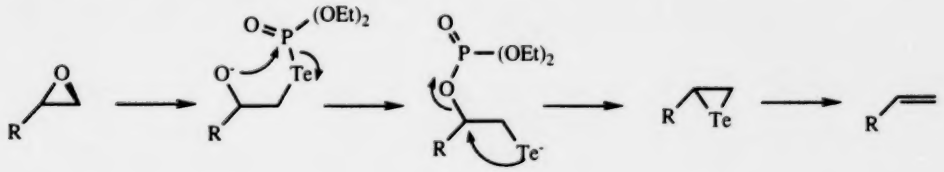
Scheme 56

The simple example using a catalytic amount of ditelluride worked well but the dithienyl ditelluride was not very efficient in the nucleoside series. Our impression is that reduction of the ArXXAr species is not a simple process. Sodium borohydride is a good reducing agent for this purpose, although an excess has to be used and it is the residual that probably is responsible for destruction of sensitive nucleoside substrates and/or products.

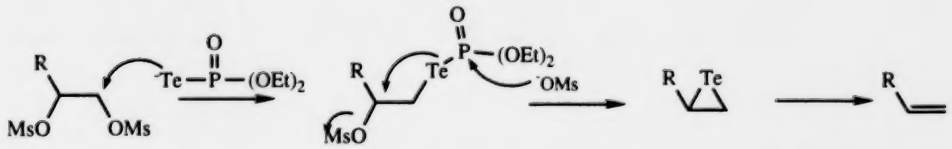
If the ArXXAr species could be incorporated into an insoluble polymer then such an excess of reducing agent could be washed away and the yields in the nucleoside series would probably be raised (see later).

Use of Sodium Diethyl Phosphorotelluroate with Dimesylates

The reaction shown in Scheme 57 (equivalent to Scheme 20) had been developed in this laboratory some years ago[47] and it provided a precedent for the process summarized in Scheme 58, which was a process that we now examined.

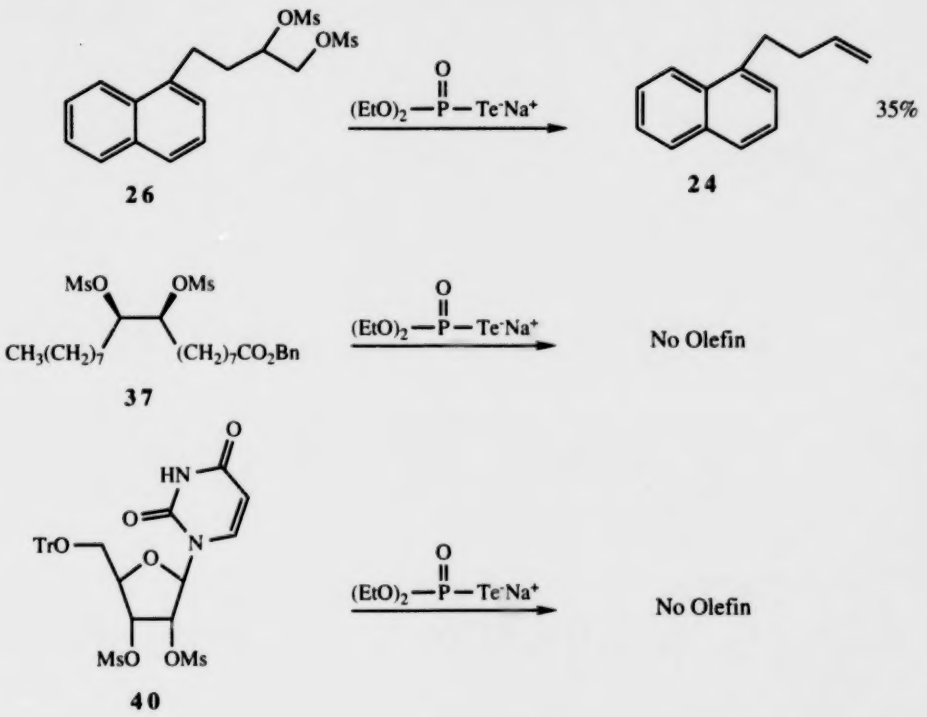


Scheme 57



Scheme 58

The tellurium reagent is easy to prepare[47] and it was tried on several substrates, as shown in Scheme 59. Only



Scheme 59

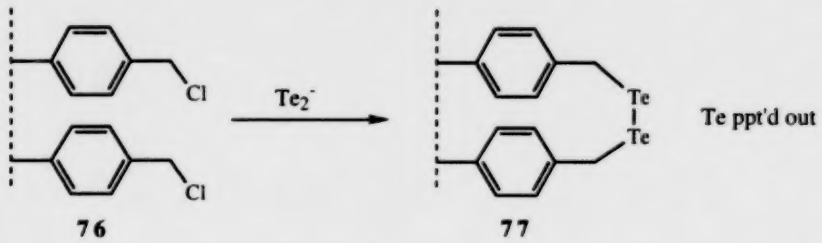
with the terminal dimesylate **26** did any olefin form, and we conclude, obviously, that this method is not general.

Polymer Supported Reagents

We carried out some exploratory studies to examine the feasibility of generating a polymer-bound reagent, *P*-ArTe$^-$ (where *P* = polymer). If such a material were available, we could wash away any excess of reducing agent so that substrates and/or products would not be destroyed.

We first treated commercial chloromethylated polystyrene [Aldrich #22,148-1] with Te^{2-} (from tellurium and Super-

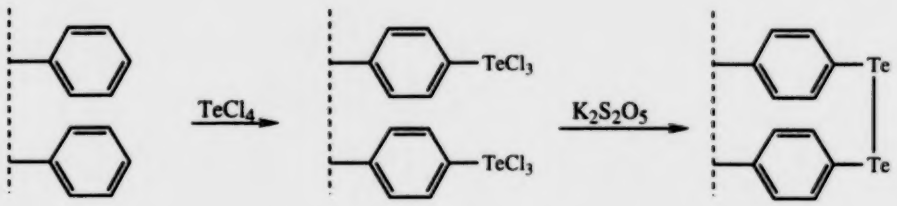
Hydride), but metallic tellurium precipitated from the reducing mixture on adding the polymer (Scheme 60).



76 **77**

Scheme 60

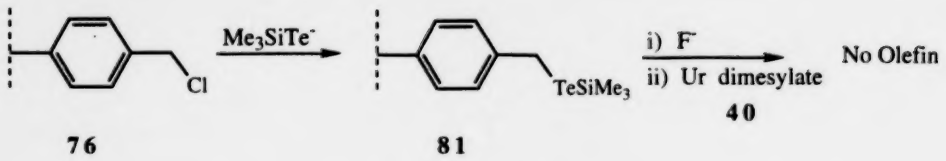
We then treated polystyrene [in the form of Biobeads S-XI (200-400 mesh) or Amberlite XE-305] with $TeCl_4$ to obtain the trichloride analogue **79**, the experiment being guided by



78 **79** **80**

Scheme 61

a literature procedure.[80] We then attempted to effect cyclization (again guided by a literature procedure[77]) to **80**. However, tellurium metal precipitated when we tried the cyclization (Scheme 61).

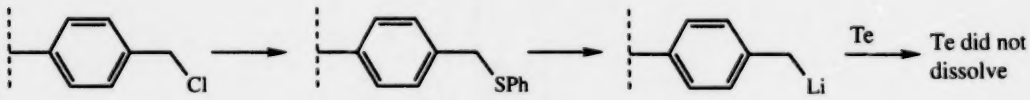


76 **81**

Scheme 62

Chloromethylated polystyrene [Aldrich #22,148-1] was then treated with ($TMSTe^-$)[81] to form **81** (or so we assume) which was then exposed to Bu_4NF to remove the TMS group and generate the telluride anion. When the uridine dimesylate was added, no olefin was detected.

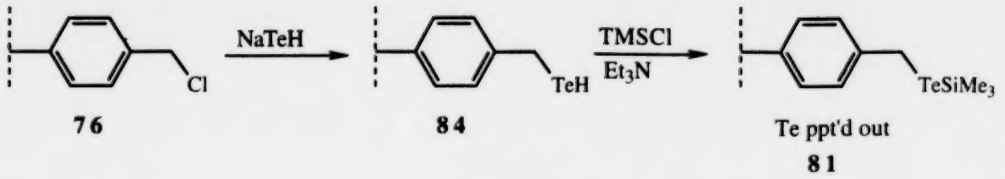
We next attempted to make a polymer-supported tellurium anion by the route shown in Scheme 63. There is precedent for the preparation of polymer-based benzyllithiums (*cf.* **83**[82]), but the tellurium did not dissolve when it was stirred with the presumed lithiated polymer.



76 **82** **83**

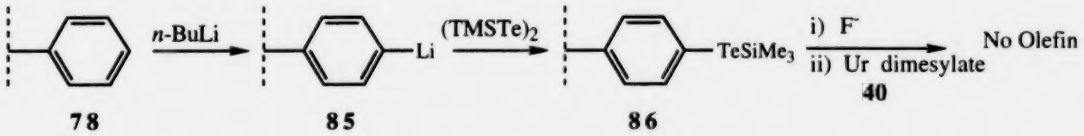
Scheme 63

Conversion of chloromethylated polystyrene **76**, into the polymer-based tellurol **84**, using NaTeH,[53] and then into the TMS protected tellurol **81** was also unsuccessful, as tellurium precipitated during the experiment (Scheme 64).



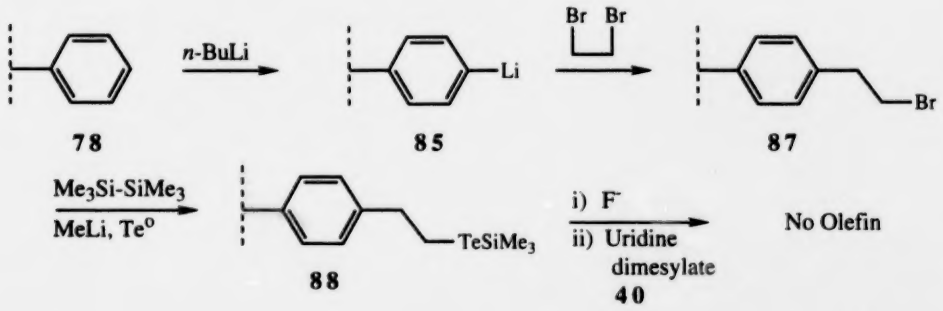
Scheme 64

Polystyrene **78** was then metalated[83] and treated with TMSTe-TeTMS,[81,84] but exposure to Bu_4NF and addition of uridine dimesylate **40** afforded no olefin (Scheme 65).



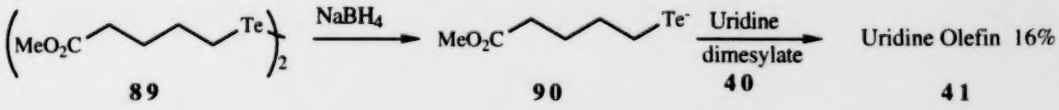
Scheme 65

Again metalation of polystyrene and treatment with ethylenedibromide, followed by substitution of the bromine for a TMSTe-group,[81] gave no olefin on addition of fluoride ion (Bu_4NF) and dimesylate **40** (Scheme 66).



Scheme 66

The above experiments were hard to follow as there is no convenient method for monitoring each stage. We decided, therefore, that it would be more convenient to make the tellurium reagent and then attach it to a polymer. To this end we prepared the ditelluride[85] **89** (Scheme 67). The

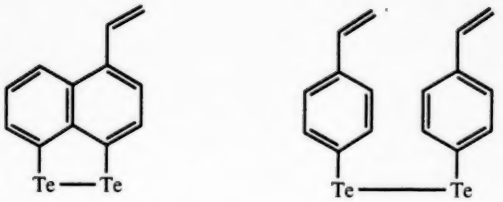


89 **90** **40** **41**

Scheme 67

ester would eventually permit attachment to a hydroxyl on a resin. Reaction of the ditelluride with $NaBH_4$ gave a colorless solution, which we took to contain the tellurium anion **90**. Addition of uridine dimesylate **40** gave the required olefin in 16% yield. The excess of $NaBH_4$ probably destroyed the dimesylate and/or the product, as before.

We conclude from these experiments that modification of a preformed polymer is unpromising and that a tellurium-containing monomer should be prepared and then polymerized in the presence of *p*-divinylbenzene (as crosslinking agent). Potentially suitable monomers are **91** and **92**[80] shown in Scheme 68, the unsubstituted ditelluride corresponding to **91** being a known compound.[86]



91 92

Scheme 68

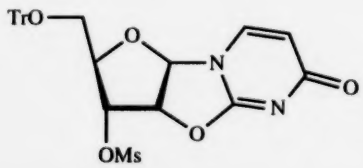
Electrochemical Experiments

As mentioned above (page 34), it would be economically desirable if tellurium metal or some aryl tellurium species could be reduced using electrochemical methods, and we made numerous attempts to implement this possibility. Our experiments are summarized in Table 2.

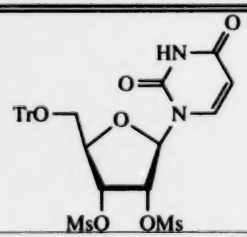
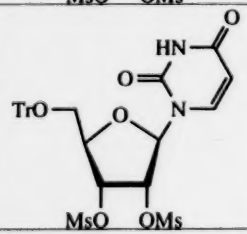
Table 2 Electrolysis Experiments

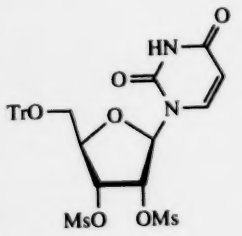
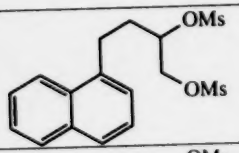
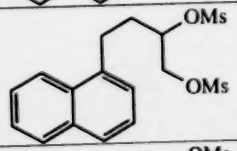
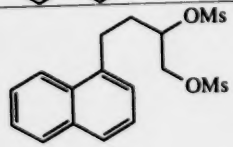
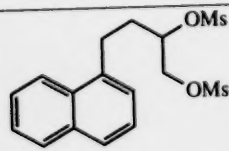
SM = starting material; CP = cyclized product; DMM = Dimethyl malonate. All reaction mixtures were stirred.

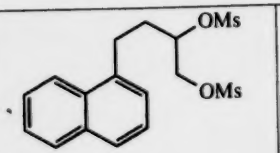
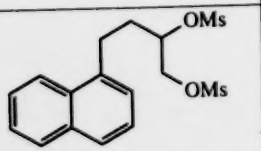
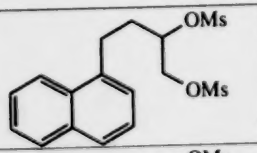
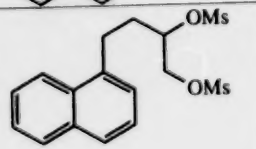
Cyclized product[88] has following structure:

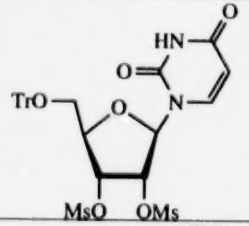
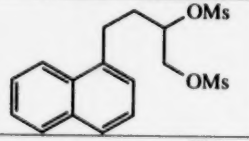
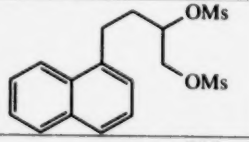
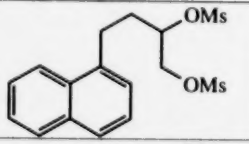
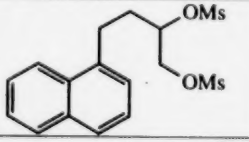
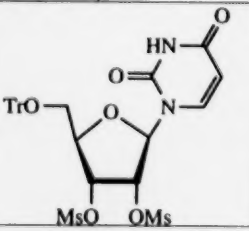


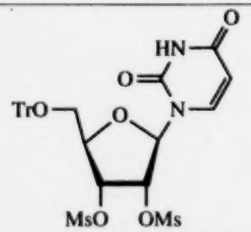
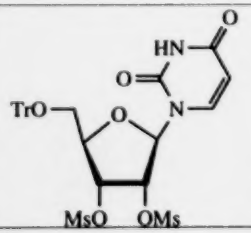
93

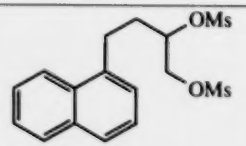
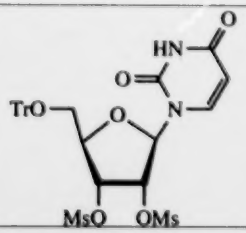
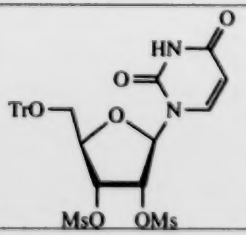
	Electrolyte	Substrate	Additive	Reagent/ conditions	Composition of reduction compartment	Pot'l & time	Yield
1	0.1 M Bu_4NPF_6 in MeCN		None	Te-graphite electrode	Added dimesylate while reduction was in progress.	-1.5 V *ca.* 5 min	73% SM 30% CP
2	0.1 M Bu_4NBr in MeCN		None	$[2,4\text{-}(MeO)_2C_6H_4Te]_2$	Ditelluride [The dimesylate was never added as the ditelluride was not reduced (no color change)]	-1.5 to -2.2 V	No reduction of ditelluride

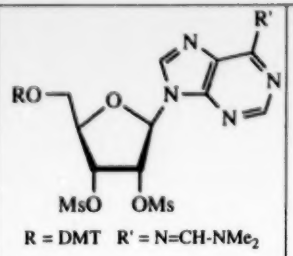
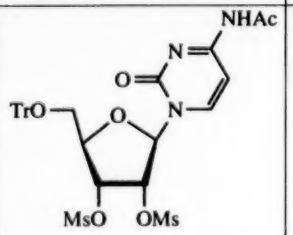
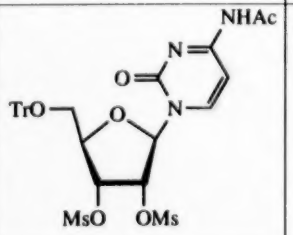
3	0.1 M Bu_4NPF_6 in MeCN		None None Ac_2O	$[2,4\text{-}(MeO)_2C_6H_4Te]_2$ (Sonication) $[2,4\text{-}(MeO)_2C_6H_4Te]_2$ (Sonication) $[2,4\text{-}(MeO)_2C_6H_4Te]_2$ (Sonication)	Dimesylate & ditelluride Ditelluride Ditelluride (then 1 drop of acetic anhydride was added along with the dimesylate)	-1.4 V -1.4 V -1.3 V	CP CP CP
4	0.1 M Bu_4NPF_6 in MeCN		None	$[2,4\text{-}(MeO)_2C_6H_4Te]_2$ (Sonication)	Ditelluride	-1.4 V	18% of olefin based on ditelluride
5	0.1 M $NaBPh_4$ in THF.		None	$[2,4\text{-}(MeO)_2C_6H_4Te]_2$ (Sonication)	Ditelluride (Dimesylate not added)	-1.5 to -1.9 V	No reduction of ditelluride
6	0.1 M Bu_4NPF_6 in THF		None	$[2,4\text{-}(MeO)_2C_6H_4Te]_2$ (Sonication)	Ditelluride (The dimesylate was added when the ditelluride solution was almost colorless)	-1.7 V	24% of olefin based on ditelluride
7	0.1 M Bu_4NPF_6 in MeCN		None	$[2,4\text{-}(MeO)_2C_6H_4Te]_2$ (Sonication)	Ditelluride (The dimesylate was added when the ditelluride solution was almost colorless)	-1.7 V	0%

8	0.1 M Bu_4NPF_6 in MeCN		None	None	Dimesylate	-1.5 V 10 min, -1.5 V 9 min, -2.1 V 9 min	56% unidentified product 91% unidentified product 100% unidentified product
9	0.1 M Bu_4NPF_6 in MeCN		DMM	$[2,4\text{-}(MeO)_2C_6H_4Te]_2$ $[2,4\text{-}(MeO)_2C_6H_4Te]_2$ $[2,4\text{-}(MeO)_2C_6H_4Te]_2$ catalytic amount	Ditelluride, dimesylate, DMM Ditelluride, dimesylate, DMM Ditelluride, dimesylate, DMM	-1.7 V -1.6 V 40 min, -1.75 V 4.5 h	SM 43% of olefin 9.5% of olefin
10	0.1 M Bu_4NPF_6 in MeCN		DMM	None	Dimesylate and DMM	-2.3 V 45 min	Unidentified reduced products
11	0.1 M Bu_4NPF_6 in THF		DMM	$[2,4\text{-}(MeO)_2C_6H_4Te]_2$	Ditelluride, dimesylate, DMM	-1.6 V 15 min, then -1.75 V 15 min, then -1.85 V 30 min	Polymer formed

12	0.1 M Bu_4NPF_6 in MeCN		DMM	$[2,4\text{-}(MeO)_2C_6H_4Te]_2$	Ditelluride, dimesylate, DMM	-1.3 V 15 min, then -1.4 V 15 min	CP
13	0.1 M Bu_4NPF_6 in MeCN		DMM	$Fe(acac)_3$	$Fe(acac)_3$, dimesylate, DMM	-0.8 V 45 min	SM
14	0.1 M Bu_4NPF_6 in MeCN		DMM	$Ni(acac)_2$	$Ni(acac)_2$, dimesylate, DMM	-1.85 V	SM
15	0.1 M Bu_4NPF_6 in MeCN		DMM	Diphenyl diselenide	Diselenide, dimesylate, DMM	-1.1 V	19% of olefin
16	0.1 M Bu_4NPF_6 in MeCN		DMM	Diphenyl diselenide	Diselenide, dimesylate, DMM at 40°C	-1.05 V	Olefin not isolated (probably not formed)
17	0.1 M Bu_4NPF_6 in MeCN		DMM	Diphenyl diselenide	Diselenide, dimesylate, DMM at 40°C	-1.05 V	CP only

18	0.1 M Bu_4NPF_6 in MeCN	-	None	$[2,4\text{-}(MeO)_2C_6H_4Te]_2$ (Sonication)	Ditelluride	-1.30V	Just cyclic voltammetry
19	0.1 M Bu_4NPF_6 in MeCN		DMM	None (Sonication)	Dimesylate Dimesylate & DMM	-1.1 V to -1.2 V -1.1 V to -1.2 V	Just cyclic voltammetry
20	0.1 M Bu_4NPF_6 in MeCN	--	DMM	$[2,4\text{-}(MeO)_2C_6H_4Te]_2$ No sonication	Ditelluride & DMM	up to -1.6 V	No reduction
21	0.1 M Bu_4NPF_6 in MeCN		DMM	$[2,4\text{-}(MeO)_2C_6H_4Te]_2$ (Sonication)	Ditelluride & DMM	-1.7 V ~25 min Mixture not totally colorless	CP
22	0.1 M Bu_4NPF_6 in MeCN	DMM	None	None	DMM	-1.4 V	Just cyclic voltammetry
23	0.1 M Bu_4NPF_6 in MeCN	$[2,4\text{-}(MeO)_2C_6H_4Te]_2$	None	None	Ditelluride	-1.85 V	Just cyclic voltammetry

24	0.1 M Bu_4NPF_6 in MeCN	DMM	None	None (Sonication) (No sonication)	DMM	-1.1 V -1.7 V	Just cyclic voltammetry
25	0.1 M Bu_4NPF_6 in MeCN	$[2,4\text{-}(MeO)_2C_6H_4Te]_2$	None	None (Stirring and sonication)	Ditelluride	-1.4 V	Just cyclic voltammetry
26	0.1 M Bu_4NPF_6 in MeCN		None	None (Stirring and sonication at 20°C)	Dimesylate	Two reduction potentials: -1.2 & -2.3 V	Just cyclic voltammetry
27	0.1 M Bu_4NPF_6 in MeCN		None	None (Stirring and sonication)	Dimesylate	Two reduction potentials: -1.25 & -2.7	Just cyclic voltammetry
28	0.1 M Bu_4NPF_6 in MeCN	Diphenyl diselenide	None	None (Stirring and sonication)	Diselenide	-1.35 V	Just cyclic voltammetry
29	0.1 M Bu_4NPF_6 in MeCN		DMM	$[2,4\text{-}(MeO)_2C_6H_4Te]_2$ (Sonication)	Ditelluride **Cyclized product was characterized**	-1.7 V	CP

30	0.1 M Bu_4NPF_6 in MeCN	 R = DMT R' = N=CH-NMe_2	None	$[2,4\text{-}(MeO)_2C_6H_4Te]_2$	Ditelluride	-1.7 V	SM
31	0.1 M Bu_4NPF_6 in MeCN		None	$[2,4\text{-}(MeO)_2C_6H_4Te]_2$	Ditelluride	-1.7 V	Unidentified product
32	0.1 M Bu_4NPF_6 in MeCN		DMM	$[2,4\text{-}(MeO)_2C_6H_4Te]_2$	Ditelluride	-1.75 V	No desired olefin

A tellurium-graphite electrode[87] was used to reduce the uridine dimesylate **40** but only the cyclized product (**93**)[88] and starting material were obtained (Table 2, entry 1). We then tried reducing the ditelluride $[2,4\text{-}(MeO)_2C_6H_4Te\text{-}]_2$ but reduction was not achieved when using 0.1 M Bu_4NBr as the electrolyte (entry 2). The electrolyte was changed to 0.1 M Bu_4NPF_6 and reduction of the ditelluride was achieved, but when the dimesylate **40** was added, the cyclized product was again obtained (entry 3). The same experiment was performed with the naphthalene dimesylate **26** and this time the olefin was obtained in 18% yield (entry 4). $NaBPh_4$ was not useful as the electrolyte (entry 5) and, when THF was used as the electrolyte solvent, a 24% yield of olefin was isolated (entry 6). Reduction of the naphthalene dimesylate **26** alone produced an unidentified product (entry 8).

The undesired products that we observed in our electrochemical experiments are possibly the result of an unknown reduced species (electrogenerated base[89]) formed in the cathode compartment. Dimethyl malonate (DMM) was added in order to quench any electrogenerated base that may have been formed, as it has been used before as a proton source[90] and, in the example of entry 9, the olefin was now obtained in 43% yield. When only the naphthalene dimesylate **26** and DMM were put under a reduction potential, unidentified reduced products were formed (entry 10). When THF was used as the electrolyte solvent with ditelluride, dimesylate, and DMM present, a polymer was the result (entry 11). In the

reduction of dimesylate **40**, in the presence of DMM, the cyclized product was again formed (entry 12). When $Fe(acac)_3$[91] or $Ni(acac)_2$[91] were added, none of the desired olefin was obtained (entries 13 and 14). When diphenyl diselenide was used as the source of nucleophile, the naphthalene dimesylate **26**, in the presence of DMM, gave a 19% yield of the olefin (entry 15). If the cell temperature was raised to 40 °C all the products evaporated when the naphthalene dimesylate **26** was used as the starting material (entry 16), but cyclized product was the result with uridine dimesylate **40** (entry 17).

Various cyclic voltammetry experiments were run (entries 18-28) to determine reduction potentials of a number of compounds. Reduction potentials seemed to be affected by stirring and sonication.[92] The reduction potentials (with stirring and sonication) of several compounds were determined as follows: DMM was -1.7 V, ditelluride **75** was -1.4 V, diphenyl diselenide was -1.35 V, uridine dimesylate **40** was -1.25 V and the naphthalene dimesylate **26** was -1.2 V. These measurements show that the dimesylates were more easily reduced than the additive (DMM), the ditelluride, or the diselenide.

Addition of the dimesylate *after* the ditelluride (or the diselenide) is reduced did not circumvent the problems caused by the unknown reduced species formed in the cathode compartment, and these degrade the dimesylate before it can react with the aryl telluride or aryl selenide anion. Other

nucleoside examples were tested, under conditions in which the ditelluride was reduced before introduction of the dimesylate, but again no olefin was obtained (entries 30-32).

In summary, we have carried out many exploratory experiments in which we tried to use Te^{2-} and $ArTe^{-}$, generated by electrochemical means. In a few cases, the desired olefin was formed, but in low yield, and the reaction conditions are clearly too harsh for the sensitive nucleoside series.

Conclusions

The reaction of nucleoside 2',3'-dimesylates with Te^{2-} constitutes an efficient method for generating the corresponding didehydrodideoxy nucleosides, and the reaction can be run on a multigram scale. Reaction of 1,2-dimesylates with $ArTe^{-}$ also leads to olefins but, as presently run, the process gives poor yields because the required excess of hydride reducing agent (used to generate the $ArTe^{-}$) destroys the nucleoside. If the $ArTe^{-}$ species were incorporated into an insoluble polymer this problem would be solved and, in addition, the deoxygenation could then be run as a flow process. Even though electrochemical reduction seems to be an elegant way of reducing tellurium or $(ArTe)_2$, the conditions studied were too harsh for the sensitive nucleoside series. Considerable further work is needed to develop this approach as well as the polymer approach, but the potential utility of such methods warrants further investigation.

Part 1 Experimental Section

General Procedures. Unless stated to the contrary, the following conditions apply: Reactions were carried out under a slight static pressure of Ar that had been purified by passage through a column (3.5 x 42 cm) of R-311 catalyst[93] and then through a similar column of Drierite. All solvents for reactions were dried, as described below. Glassware was dried in an oven for at least 3 h before use (120 °C) and either cooled in a desiccator over Drierite, or assembled quickly, sealed with rubber septa, and allowed to cool under a slight static pressure of Ar. Reaction mixtures were stirred by Teflon-coated magnetic stirring bars.

Hexane used for chromatography was distilled before use.

Products were isolated from solution by solvent removal under water-aspirator vacuum at, or below, room temperature, using a rotary evaporator.

Microliter syringes were washed with water and acetone, using a suction device to draw the solvents through. Then air was sucked through for 1 min. The solution to be dispensed was drawn up and expelled, and this operation was repeated several times before drawing up the sample to be used. Cannula transfers were always done under slight pressure (Ar), not by suction.

Commercial thin layer chromatography (TLC) plates (silica gel, Merck 60F-254) were used. Spots were detected by spraying the plate with a solution of phosphomolybdic

acid[94] or *p*-anisaldehyde,[95] followed by charring with a heat gun, or by examination under UV light. Silica gel for flash chromatography was Merck type 60 (230-400 mesh).

Dry solvents were prepared under an inert atmosphere and transferred by syringe or cannula. Dry tetrahydrofuran (THF) and Et_2O were distilled from sodium and benzophenone ketyl. Dry PhH was distilled from sodium. Dry Et_3N, CH_2Cl_2, MeOH, MeCN, and pyridine were distilled from CaH_2.

FT-IR measurements were made as casts from the specified solvent using potassium bromide plates.

Mass spectra were recorded with AEI Models MS-12, MS-50, MS9 (modified), or Kratos MS50 (modified) mass spectrometers.

Microanalyses were performed by the microanalytical laboratory of this Department. Compounds isolated by flash chromatography were homogeneous by tlc and, unless otherwise stated, were pure as judged by high field ^1H NMR spectra.

Preparation of selenium and tellurium reagents

Preparation of Sodium Telluride (Na_2Te).[96]

A 500-mL three-neck round-bottomed flask was charged with Te powder (200 mesh, 2.205 g, 17.28 mmol) and a stirring bar. Na (0.794 g, 34.5 mmol) was placed in a sidearm addition tube, and the central neck of the flask was fitted with a condenser charged with dry-ice/acetone and closed by a septum carrying both an entry needle for Ar and an exit needle leading to an oil bubbler. The third neck of the

flask was temporarily closed by a septum, and the flask was flushed with Ar. The septum in the third neck was removed and immediately replaced by an adaptor (fitted with a tap) connected to a tank of liquid NH_3. The flask was now cooled with dry-ice/MeCN, and NH_3 was led in until *ca.* 200 mL had collected. The ammonia inlet was closed and a slow stream of Ar was maintained. The stirrer was started and the Na was added portionwise by tapping the sidearm addition tube. The mixture changed from red to bluish-green to white, by which stage formation of Na_2Te was complete. The cooling bath was removed, and stirring was continued overnight, during which period the coolant in the condenser attained room temperature and the NH_3 evaporated. The resulting beige Na_2Te (*ca.* 100% yield) was transferred in an Ar-filled glove bag to a storage flask.

Preparation of Sodium Selenide (Na_2Se).[97]

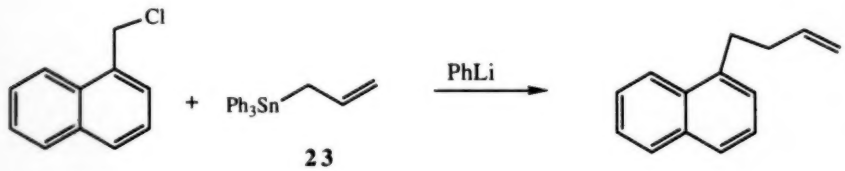
A 500-mL three-neck round-bottomed flask was charged with Se powder (325 mesh, 2.847 g, 36.06 mmol) and a stirring bar. Na (1.741 g, 75.73 mmol) was placed in a sidearm addition tube, and the central neck of the flask was fitted with a condenser charged with dry-ice/acetone and closed by a septum carrying both an entry needle for Ar and an exit needle leading to an oil bubbler. The third neck of the flask was temporarily closed by a septum, and the flask was flushed with Ar. The septum in the third neck was removed and immediately replaced by an adaptor (fitted with a tap)

connected to a flask containing a small amount (*ca.* 1 g) of Na. This latter flask was in turn connected to a tank of liquid NH_3, and was then cooled with dry-ice/MeCN. NH_3 was led in until *ca.* 200 mL had collected. The cooling bath was removed and the NH_3 was distilled into the reaction vessel, which was cooled with dry-ice/MeCN. The ammonia inlet was removed and a slow stream of Ar was maintained. The stirrer was started and the Na was added portionwise by tapping the sidearm addition tube. The mixture changed color and eventually became white, by which stage formation of Na_2Se was complete. The cooling bath was removed and stirring was continued overnight, during which period the coolant in the condenser attained room temperature and the NH_3 evaporated. The resulting slightly orange Na_2Se (*ca.* 100% yield) was transferred in an Ar-filled glove bag to a storage flask.

Preparation of starting diols

4-(1-Naphthyl)-1,2-butanediol (25).

(a) 1-(3-Butenyl)naphthalene (24).[98]

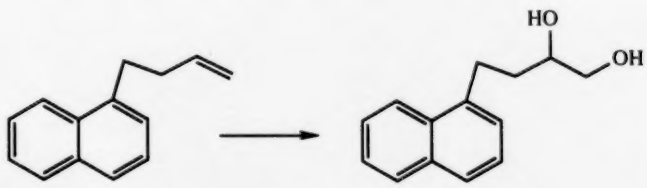


22 23 24

Compound **24** has been reported before,[98] but was made by the following different method.

PhLi (2 M in 7:3 cyclohexane-Et_2O, 1.7 mL, 3.3 mmol) was added to a stirred solution of allyltriphenyltin[50] (1.183 g, 3.030 mmol) in Et_2O (20 mL). The mixture was stirred for 30 min and 1-(chloromethyl)naphthalene (**22**)[99] (0.534 g, 3.03 mmol) in Et_2O (20 mL) was added. The solution, which changed color from orange to white, was stirred for 24 h. The mixture was filtered through Celite with EtOAc, and the filtrate was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 × 30 cm), using hexane, gave **24** (0.201 g, 37%) as a pure (^1H NMR, 300 MHz), colorless oil: FTIR (neat) unexceptional; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.40-2.60 (m, 2 H), 3.10-3.22 (m, 2 H), 4.95-5.15 (m, 2 H), 5.85-6.05 (m, 1 H), 7.25-8.10 (m, 7 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 32.53, 34.86, 114.97, 123.79, 125.57, 125.81, 125.99, 126.71, 127.22, 128.85, 131.92, 133.96, 137.99, 138.30; exact mass *m/z* calcd for $C_{14}H_{14}$ 182.1095, found 182.1096.

(b) 4-(1-Naphthyl)-1,2-butanediol (25).

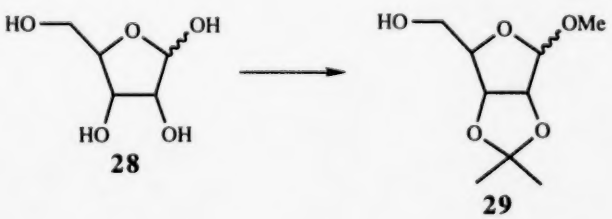


24 **25**

OsO_4 (1.7 mL, 2.5% w/w solution of OsO_4 in *t*-BuOH) was added to a stirred solution of 1-(3-butenyl)naphthalene (**24**) (1.121 g, 6.153 mmol) and NMO (1.033 g, 7.652 mmol) in acetone (30 mL) and water (15 mL). Stirring at room temperature was continued for 43 h. EtOAc (100 mL) was then added and the organic layer was washed with water (1 x 100 mL) and aqueous Na_2SO_3 (10%, 2 x 50 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (5 x 20 cm), using 7:3 EtOAc-hexane, gave **25** (1.200 g, 90%) as a pure (^{1}H NMR, 200 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 3360 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.70-2.05 (m, 4 H), 3.05-3.45 (m, 2 H), 3.50 (dd, *J* = 11.0, 7.0 Hz, 1 H), 3.71 (dd, *J* = 11.0, 3.0 Hz, 1 H), 3.75-3.95 (m, 1 H), 7.30-7.60 (m, 4 H), 7.60-7.80 (m, 1 H), 7.80-7.95 (m, 1 H), 7.95-8.20 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 28.93, 34.02, 66.86, 71.89, 123.74, 125.55, 125.58, 125.92, 126.07, 126.82, 128.85, 131.81, 133.97, 137.89; exact mass *m/z* calcd for $C_{14}H_{16}O_2$ 216.1151, found 216.1151.

Methyl 5-*O*-benzyl-β-D-ribofuranoside (31).[100]

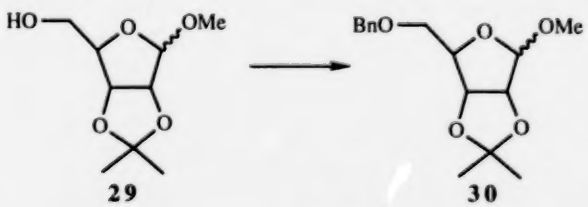
(a) Methyl 2,3-*O*-Isopropylidene-D-ribofuranoside (29).[101, 102]



The literature procedure[101] was followed, except that the workup was different.

H_2SO_4 (0.17 mL) was added to a stirred mixture of D-ribose (**28**) (4.118 g, 27.43 mmol), anhydrous $CuSO_4$ (9.16 g, 51.6 mmol), MeOH (4.2 mL), and acetone (78 mL). The stirred mixture was kept at 40 °C for 24 h, cooled, and filtered through Celite with acetone. $Ca(OH)_2$ (2 g) was added and the mixture was stirred for 0.5 h and again filtered through Celite. The filtrate was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (4 × 30 cm), using first 3:7 EtOAc-hexane and then 1:1 EtOAc-hexane, gave **29** (3.04 g, 54%) as a pure (^1H NMR 400 MHz), colorless oil: FTIR (CH_2Cl_2, cast) 3600-3200 cm^{-1}; ^1H NMR identical to that reported;[102] ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 24.70, 26.35, 55.51, 64.00, 81.49, 85.82, 88.36, 109.98, 112.12; exact mass *m/z* calcd for $C_8H_{13}O_5$ (M - CH_3) 189.0763, found 189.0762.

(b) Methyl 5-*O*-Benzyl-2,3-*O*-isopropylidene-D-ribofuranoside (30).[103]

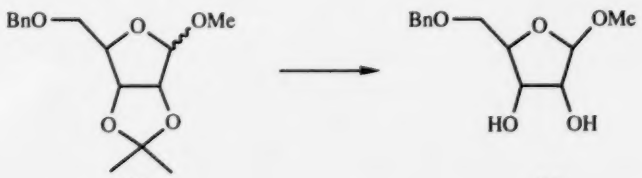


29 **30**

The literature procedure[103] was followed, except that the workup was different and no spectral data were available previously.

BnCl (8.1 mL, 70 mmol) was added dropwise to a stirred mixture of **29** (2.40 g, 11.7 mmol), KOH (9.22 g), and PhMe (24 mL). The mixture was stirred at 80 °C for 44 h, and then cooled to room temperature. Water (160 mL) and EtOAc (150 mL) were added, and the organic phase was washed with water (3 × 25 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (4 × 30 cm), using 1:9 EtOAc-hexane, gave **30** (3.24 g, 93%) as a pure (^1H NMR, 300 MHz), colorless oil: FTIR (CH_2Cl_2, cast) unexceptional; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.32 (s, 3 H), 1.48 (s, 3 H), 3.29 (s, 3 H), 3.40-3.58 (m, 2 H), 4.32-4.42 (m, 1 H), 4.50-4.60 (m, 3 H), 4.65-4.70 (m, 1 H), 4.96 (ap s, 1 H), 7.28-7.38 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 25.05, 26.49, 54.80, 71.13, 73.27, 82.17, 85.19 (two overlapping signals), 109.31, 112.39, 127.70 (two overlapping signals), 128.40, 138.04; exact mass *m/z* calcd for $C_{15}H_{19}O_5$ (M - CH_3) 279.1232, found 279.1231.

(c) Methyl 5-*O*-benzyl-β-D-ribofuranoside (31).[100]



30 **31**

The literature procedure[100] was followed, except that the workup was different and no spectral data were available previously.

H_2SO_4 (0.9 mL) was added to a stirred solution of **30** (0.406 g, 1.38 mmol) in MeOH (8.4 mL) and water (1.65 mL). The mixture was stirred at 80 °C for 2.5 h, and then cooled. $Ca(OH)_2$ (0.25 g) was added. The mixture was then stirred for 1 h and filtered through Celite with MeOH. The organic layer was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 × 40 cm), using 7:3 EtOAc-hexane, gave **31** (0.242 g, 69%) as a pure (^{1}H NMR, 200 MHz), colorless oil: FTIR (CH_2Cl_2, cast) 3600-3200 cm^{-1}; ^{1}H NMR identical to that reported;[100] ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 55.13, 71.98, 72.75, 73.49, 74.95, 81.86, 108.29, 127.80 (two overlapping signals), 128.44, 137.88; CIMS *m/z* calcd for $C_{13}H_{22}NO_5$ ($M + NH_4^+$) 272, found 272.

Benzyl (9*S,10*R**)-9,10-dihydroxyoctadecanoate (36).**

(a) Oleic acid benzyl ester (35).[104]

34 **35**

The following procedure is different from that given in the literature.[104]

BnOH (2.59 g, 24.0 mmol) was added to a stirred solution of oleic acid (**34**) (5.70 g, 20.2 mmol), and $TsOH•H_2O$ (0.2 g,

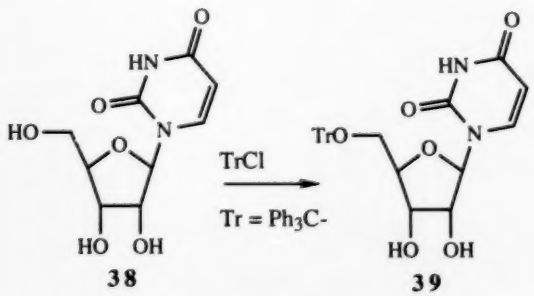
0.6 mmol) in PhH (20 mL). The mixture was refluxed for 22 h using a Dean-Stark apparatus. Evaporation of the solvent and flash chromatography of the residue over silica gel (6 × 40 cm), using first hexane and then 1:9 EtOAc-hexane, gave **35** (7.55 g, 100%) as a pure (^{1}H NMR, 200 MHz), colorless oil: FTIR (CH_2Cl_2, cast) 2925, 2853, 1739 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.80-0.98 (m, 3 H), 1.08-1.45 (m, 20 H), 1.52-1.75 (m, 2 H), 1.90-2.01 (m, 4 H), 2.30-2.42 (ap t, *J* = 8 Hz, 2 H), 5.12 (ap s, 2 H), 5.30-5.40 (m, 2 H), 7.30-7.42 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 14.13, 22.71, 24.98, 27.26, 29.02, 29.13, 29.17, 29.28, 29.36, 29.49, 29.56, 29.62, 29.80, 31.94, 34.36, 66.07, 128.17 (two overlapping signals), 128.55, 129.77, 130.02, 136.21, 173.64; CIMS *m/z* calcd for $C_{25}H_{40}O_2$ 372, found 372.

(b) Benzyl (9*S,10*R**)-9,10-dihydroxyoctadecanoate (36).**

OsO_4 (3.95 mL, 2.5% w/w solution of OsO_4 in *t*-BuOH) was added to a solution of oleic acid benzyl ester (**35**) (5.658 g, 15.18 mmol) and NMO (3.749 g, 27.77 mmol) in acetone (500 mL) and water (38 mL). The mixture was stirred at room temperature for 24 h, and then evaporated at room temperature to *ca*. 100 mL. EtOAc (200 mL) was added, and the organic

layer was washed with water (1 x 200 mL) and aqueous Na_2SO_3 (10%, 3 x 200 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (10 x 50 cm), using 3.2:96.8 MeOH-$CHCl_3$, gave **36** (4.432 g, 72%) as a pure (^1H NMR, 400 MHz), colorless oil: FTIR ($CHCl_3$, cast) 3280, 1735 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.80-1.00 (m, 3 H), 1.20-1.58 (m, 24 H), 1.58-1.75 (m, 2 H), 1.95 (br s, 2 H), 2.35 (t, J = 7.2, 2 H), 3.50-3.70 (m, 2 H), 5.11 (s, 2 H), 7.28-7.45 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 14.13, 22.70, 24.93, 25.95, 26.06, 29.06, 29.18, 29.31, 29.46, 29.59, 29.73, 31.21, 31.30, 31.91, 34.34, 66.12, 74.69, 74.76, 128.20 (two overlapping signals), 128.58, 136.70, 173.70; exact mass *m/z* calcd for $C_{25}H_{38}O_2$ (M - $2H_2O$) 370.2873, found 370.2869; mass (CI) *m/z* calcd for $C_{25}H_{42}O_4$ 406, found 424 (M + 18).

5'-*O*-(Triphenylmethyl)uridine (39).[105]

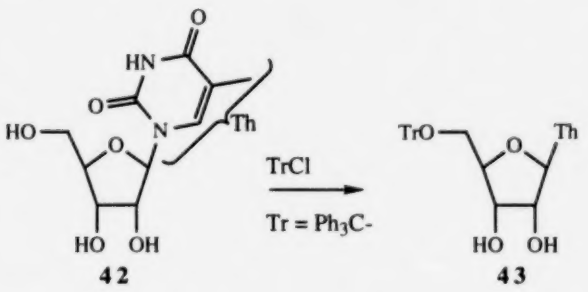


38 **39**

The literature procedure[105] was followed, but using a different workup.

Uridine (**38**) (155 mg, 0.634 mmol), trityl chloride (199 mg, 0.715 mmol), and a small stirring bar were placed in a dry round-bottomed flask fused onto a reflux condenser. The flask was closed with a septum and flushed with Ar. Pyridine (1.90 mL) was injected and the mixture was stirred at room temperature for 48 h. The mixture was then heated for 0.5 h (oil bath at 100 °C), cooled, and poured onto ice (*ca.* 25 g). The gummy product was filtered off, washed with water, and dissolved in acetone. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 30 cm), using 5:95 MeOH-CH_2Cl_2, gave pure (tlc,silica, 5:95 MeOH-CH_2Cl_2) **39** (250 mg, 81%): FTIR (CH_2Cl_2, cast) 3600-3200, 1691 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.35-3.62 (m, 3 H), 4.10-4.25 (m, 1 H), 4.30-4.52 (m, 2 H), 5.25-5.38 (m, 1 H), 5.48-5.65 (br s, 1 H), 5.85-5.93 (m, 1 H), 7.18-7.50 (m, 15 H), 7.95-8.06 (ap d, J = 8 Hz, 1 H), 10.35-10.45 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 62.01, 69.71, 75.59, 83.80, 87.67, 90.88, 102.24, 127.48,* 127.77,* 128.09,* 140.38, 143.24,* 151.09, 163.77 (the four starred signals represent 18 carbons in the trityl group); exact mass *m/z* calcd for $C_{19}H_{15}$ (M - $C_9H_{11}N_2O_6$) 243.1174, found 243.1171; exact mass *m/z* calcd for $C_9H_{11}N_2O_6$ (M - $C_{19}H_{15}$) 243.0617, found 243.0620; FABMS *m/z* calcd for $C_{28}H_{27}N_2O_6$ (M + H) 487, found 487.

5-Methyl-5'-*O*-(triphenylmethyl)uridine (43).[106]



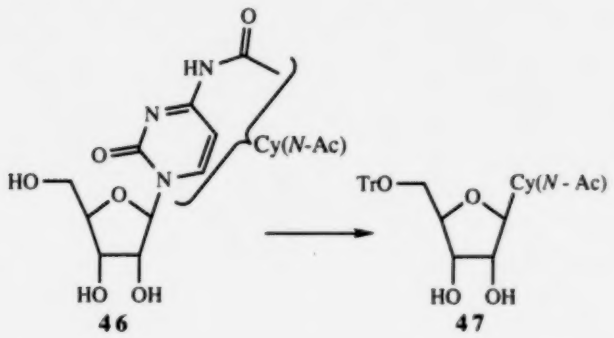
42 **43**

The literature procedure[106] was followed:

5-Methyluridine (**42**) (194 mg, 0.753 mmol), trityl chloride (234 mg, 0.839 mmol), and a small stirring bar were placed in a dry round-bottomed flask fused onto a reflux condenser (one piece). The flask was closed with a septum and flushed with Ar. Pyridine (2.2 mL) was injected and the mixture was stirred at room temperature for 24 h. The mixture was poured onto ice (*ca.* 25 g) and the gummy product was filtered off, washed with water and dissolved in acetone. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 25 cm), using 5:95 MeOH-CH_2Cl_2, gave **43** (221 mg, 59%) as a pure (^{1}H NMR, 200 MHz), colorless oil: FTIR (CH_2Cl_2, cast) 3600-3200, 1691 cm^{-1}; ^{1}H NMR (acetone-d_6, 200 MHz) δ 1.48 (ap s, 3 H), 3.35-3.48 (m, 2 H), 4.08-4.18 (m, 1 H), 4.32-4.48 (m, 3 H), 4.68-4.77 (m, 1 H), 5.90-6.02 (d, J = 4 Hz, 1 H), 7.22-7.62 (m, 16 H), 10.02 (br s, 1 H); ^{13}C NMR (pyridine-d_5, 100.6 MHz) δ 12.41, 64.55, 71.50, 75.36, 84.10, 87.51, 90.06, 110.72, 127.61,* 128.38,* 129.17,* 136.05, 144.37,* 152.13, 164.83 (the four starred

signals represent 18 carbons in trityl group); exact mass *m/z* calcd for $C_{29}H_{26}N_2O_5$ (M - H_2O) 482.1842, found 482.1843.

N-Acetyl-5'-O-(triphenylmethyl)cytidine (47).[107]



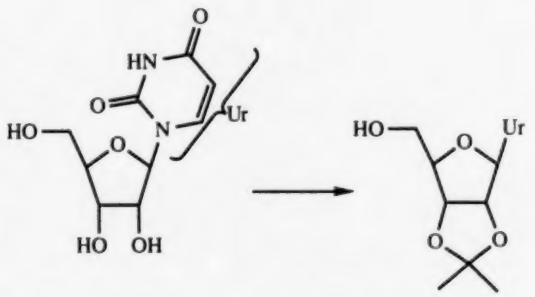
A very similar procedure (reaction temperature 110 °C) has been reported[107] but the yield was only 14%.

N-Acetylcytidine **46**[107] (1.000 g, 3.506 mmol), trityl chloride (1.075 g, 3.856 mmol) and a small stirring bar were placed in a dry round-bottomed flask fused onto a reflux condenser (one piece). The flask was closed with a septum and flushed with Ar. Pyridine (10 mL) was injected and the mixture was stirred at room temperature for 36 h. The mixture was evaporated, diluted with CH_2Cl_2, and again evaporated. The gummy residue was washed with water and the residue was dissolved in acetone. The solution was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (4.5 x 30 cm), using 7:93 MeOH-CH_2Cl_2, gave **47** (1.475 g, 80%) as a pure (^{1}H NMR, 200 MHz), colorless oil: FTIR (CH_2Cl_2, cast) 3600-3200, 1656 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200

MHz) δ 2.25 (s, 3 H), 3.30-3.55 (m, 3 H), 4.30-4.48 (m, 3 H), 5.58 (br s, 1 H), 5.80-5.90 (m, 1 H), 7.20-7.40 (m, 16 H), 8.10-8.20 (d, J = 8 Hz, 1 H), 8.55-8.77 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 24.81, 62.12, 69.88, 76.02, 84.04, 87.44, 92.24, 96.98, 127.32,* 127.98,* 128.57,* 143.18,* 144.73, 156.23, 162.64, 170.74 (the four starred signals represent 18 carbons in trityl group); exact mass m/z calcd for $C_{30}H_{27}N_3O_5$ (M - H_2O) 509.1951, found 509.1943.

5'-*O*-Acetyluridine (56).[108]

(a) 2',3'-*O*-Isopropylideneuridine (55).[108]



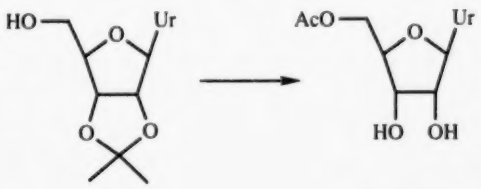
38 **55**

The literature procedure[108] was followed, but with a different workup.

Uridine **38** (1.000 g, 4.095 mmol), TsOH•H_2O (101 mg, 0.532 mmol), and a small stirring bar were placed in a dry round-bottomed flask fused onto a reflux condenser. The flask was closed with a septum and flushed with Ar. Dry acetone (15 mL) and 2,2-dimethoxypropane (3.22 mL) were injected into the flask and the mixture was stirred at room

temperature for 15 h. Solid sodium methoxide was then added until the solution became slightly basic (moist litmus paper). The mixture was evaporated at room temperature, and flash chromatography of the residue over silica gel (3 x 30 cm), using 5:95 MeOH-CH_2Cl_2, gave **55** (1.058 g, 91%) as a pure (^{1}H NMR, 200 MHz), colorless oil: FTIR (CH_2Cl_2, cast) 3600-3300, 3300-3140, 1692 cm^{-1}; ^{1}H NMR (acetone-d_6, 200 MHz) δ 1.33 (s, 3 H), 1.53 (s, 3 H), 3.72-3.82 (ap t, *J* = 7.6, 3.8 Hz, 2 H), 4.00-4.40 (m, including br s at δ 4.23, 2 H in all), 4.82-5.00 (m, 2 H), 5.55-5.65 (m, 1 H), 5.88-5.95 (d, *J* = 3.6 Hz, 1 H), 7.85-7.88 (d, *J* = 8 Hz, 1 H), 9.60-10.30 (br s, 1 H); ^{13}C NMR (acetone-d_6, 50.3 MHz) δ 25.57, 27.52, 63.06, 67.97, 80.96, 84.49, 87.43, 95.58, 102.90, 142.96, 150.90, 160.13; exact mass *m/z* calcd for $C_{12}H_{16}N_2O_6$ 284.1008, found 284.1011.

(b) 5'-*O*-Acetyluridine (56).[108]



55 **56**

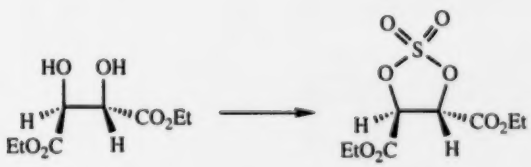
The literature procedure[108] was followed, but with a different workup. Spectroscopic data were not reported.

2',3'-*O*-Isopropylideneuridine (**55**) (0.500 g, 1.76 mmol) and a small stirring bar were placed in a round-bottomed

flask. The flask was sealed with a septum and flushed with Ar. Pyridine (1 mL) and Ac_2O (0.11 mL) were injected and the mixture was stirred at room temperature for 15 h. MeOH (0.37 mL) was added and the mixture was stirred for 1 h. The solution was evaporated from a 1:1 mixture of EtOH and water (2 x 15 mL). The product was dissolved in formic acid (60%, 1.44 mL), and the solution was stirred for 3 h and then evaporated. Flash chromatography of the residue over silica gel (2 x 30 cm), using 7:93 MeOH-CH_2Cl_2, gave **56** (0.417 g, 82%) as a pure (^{1}H NMR, 400 MHz), colorless oil: ^{1}H NMR (acetone-d_6, 200 MHz) δ 2.08 (s, 3 H), 4.10-4.38 (m, 5 H), 4.38-4.58 (br s, 1 H), 4.60-4.85 (br s, 1 H), 5.60-5.70 (d, J = 8 Hz, 1 H), 5.82-5.92 (d, J = 4 Hz, 1 H), 7.62-7.72 (d, J = 8 Hz, 1 H), 9.75-10.25 (br s, 1 H).

Preparation of dimesylates and other substrates for deoxygenation

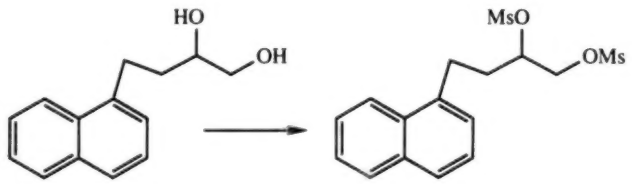
Diethyl 1,3,2-Dioxathiolane-4,5-dicarboxylate 2,2-dioxide (20).[48]



19 **20**

The Sharpless procedure[48] was used on diethyl tartrate **19**[99] (0.552 g, 2.68 mmol), and gave **20**[48] (0.339 g, 56%) as a pure (^{1}H NMR, 400 MHz), colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.25-1.50 (t, *J* = 8 Hz, 6 H), 4.30-4.50 (q, *J* = 8 Hz, 4 H), 5.48 (ap s, 2 H).

4-(1-Naphthyl)butane-1,2-diol dimethanesulfonate (26).

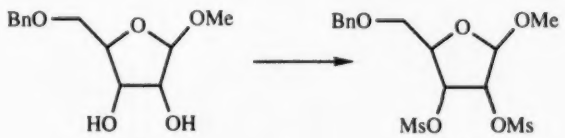


25 **26**

$MeSO_2Cl$ (1.6 mL, 20 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a stirred and cooled (0 °C) solution of 4-(1-naphthyl)-1,2-butanediol (**25**) (1.123 g, 5.192 mmol) and pyridine (3.4 mL, 41 mmol) in CH_2Cl_2 (10 mL) (Ar atmosphere). The ice bath was removed and stirring was continued for 16 h. The mixture was poured onto ice (*ca.* 50 g) and extracted with EtOAc (1 x 100 mL). The organic extract was washed with aqueous $CuSO_4$ (10%, 2 x 50 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 x 30 cm), using 1:1 EtOAc-hexane, gave **26** (1.849 g, 96%) as a pure (^{1}H NMR, 200 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 1356, 1173 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.05-2.40 (m,2 H), 3.0-3.10 (s, 3 H), 3.10-3.15 (s, 3 H), 3.15-3.45 (m, 2 H), 4.30 (dd, *J* = 11.0, 6.0 Hz, 1 H), 4.44 (dd, *J* = 11.0, 3.0 Hz, 1

H), 4.95-5.10 (m, 1 H), 7.30-7.65 (m, 4 H), 7.70-7.80 (m, 1 H), 7.80-7.93 (m, 1 H), 7.93-8.05 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 28.25, 32.08, 37.74, 38.90, 69.46, 78.66, 123.26, 125.63, 125.76, 126.30 (two overlapping signals), 127.40, 129.01, 131.49, 134.00, 135.99; exact mass *m/z* calcd for $C_{16}H_{20}O_6S_2$ 372.0702, found 372.0694.

Methyl 5-*O*-Benzyl-2,3-di-*O*-mesyl-β D-ribofuranoside (32).

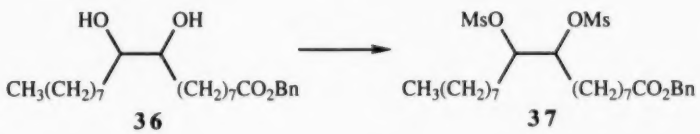


31 **32**

$MeSO_2Cl$ (1.6 mL, 20 mmol) in CH_2Cl_2 (10 mL), was added dropwise to a stirred and cooled (0 °C) solution of methyl 5-*O*-benzyl-β-D-ribofuranoside (**31**) (1.302 g, 5.122 mmol) and pyridine (3.3 mL, 41 mmol) in CH_2Cl_2 (10 mL) (Ar atmosphere). The ice bath was removed and stirring was continued for 24 h. The mixture was poured onto ice (*ca.* 50 g) and extracted with EtOAc (100 mL). The organic extract was washed with aqueous $CuSO_4$ (10%, 2 x 50 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 x 30 cm), using 30:70 EtOAc-hexane, gave **32** (1.963 g, 93%) as a pure (^1H NMR, 300 MHz), colorless oil: FTIR (CH_2Cl_2, cast) 1384, 1180 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.97 (s, 3 H), 3.15 (s, 3 H), 3.41 (s, 3 H), 3.62 (dd, *J* = 10.5, 5.0 Hz, 1 H), 3.70

(dd, J = 10.5, 4.4 Hz, 1 H), 4.40 (ddd, J = 6.5, 5.0, 4.5 Hz, 1 H), 4.58 (q, J = 17.0, 12.0 Hz, 2 H), 4.98 (dd, J = 5.0 Hz, 1.5, 1 H), 5.08 (d, J = 1.5 Hz, 1 H), 5.20 (dd, J = 6.5, 5.0 Hz, 1 H), 7.28-7.45 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 38.12, 38.50, 55.65, 69.79, 73.74, 77.26, 79.15, 79.79, 105.68, 127.91, 128.02, 128.54, 137.49; exact mass *m/z* calcd for $C_{15}H_{22}O_9S_2$ 410.0706, found 410.0734.

Benzyl (9*S,10*R**)-9,10-Dihydroxyoctadecanoate dimethanesulfonate (37).**

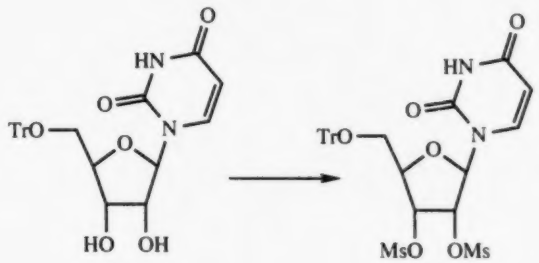


36 **37**

$MeSO_2Cl$ (1.8 mL, 23 mmol) in $CHCl_3$ (4 mL), was added dropwise to a stirred and cooled (0 °C) solution of benzyl (9*S**,10*R**)-9,10-dihydroxyoctadecanoate (**36**) (1.170 g, 2.878 mmol) and pyridine (3.80 mL, 46.0 mmol) in $CHCl_3$ (11 mL) (Ar atmosphere). The ice bath was removed and stirring was continued for 40 h. The mixture was poured onto ice (*ca.* 50 g) and extracted with $CHCl_3$ (200 mL). The organic extract was washed with aqueous $CuSO_4$ (10%, 2 x 100 mL) and aqueous NaOH (0.5 M, 1 x 50 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 x 30 cm), using 5:95 MeOH-$CHCl_3$, gave **37** (1.532 g, 95%), which contained a trace impurity (^1H NMR, 200 MHz), (signals at δ 3.0 and δ 3.1) but was suitable for the next stage: FTIR

($CHCl_3$, cast) 1735, 1357, 1175 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.78-0.98 (m, 3 H), 1.18-1.88 (m, 26 H), 2.35 (t, J = 7.0 Hz, 2 H), 3.09 (s, 6 H), 4.68-4.88 (m, 2 H), 5.10 (s, 2 H), 7.25-7.38 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 14.07, 22.50, 22.61, 24.81, 25.36, 25.45, 28.91 (three overlapping signals), 29.14, 29.27, 29.58, 29.65, 31.77, 34.22, 38.82 (two overlapping signals), 66.06, 82.81, 82.91, 128.15 (two overlapping signals), 128.54, 136.14, 173.52; exact mass *m/z* calcd for $C_{27}H_{47}O_8S_2$ (M + H) 563.2714, found 563.2732.

5'-*O*-(Triphenylmethyl)uridine 2',3'-dimethanesulfonate (40).[109]



39 **40**

(a) Small scale

$MeSO_2Cl$ (1.45 mL, 18.7 mmol) in CH_2Cl_2 (8 mL) was added dropwise to a stirred and cooled (0 °C) solution of 5'-*O*-(triphenylmethyl)uridine (**39**) (2.281 g, 4.690 mmol) and pyridine (3.0 mL, 38 mmol) in CH_2Cl_2 (10 mL) (Ar atmosphere). The ice bath was removed and stirring was continued for 48 h. The mixture was poured onto ice (*ca.* 100 g) and extracted with EtOAc (2 x 100 mL). The organic extract was washed with

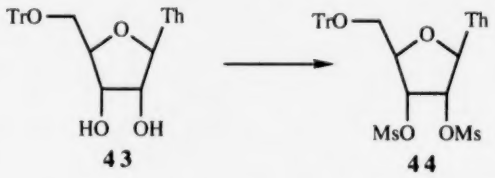
water (2 x 100 mL), aqueous NaOH (0.5 M, 1 x 50 mL), and aqueous $CuSO_4$ (10%, 1 x 100 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (4 x 30 cm), using 3:97 MeOH-CH_2Cl_2, gave pure (^1H NMR, 200 MHz) **40** (2.603 g, 86%): FTIR (CH_2Cl_2, cast) 1694, 1364, 1179 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.10 (s, 3 H), 3.21 (s, 3 H), 3.50-3.75 (m, 2 H), 4.25-4.50 (m, 1 H), 5.25-5.65 (m, 3 H), 6.02 (d, *J* = 3.0 Hz, 1 H), 7.10-7.60 (m, 15 H), 7.72 (d, *J* = 8.0 Hz, 1 H), 9.32 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 38.62, 38.86, 60.87, 73.58, 78.24, 80.93, 88.18, 88.43, 103.20, 127.69, 128.24, 128.73, 139.95, 142.68, 150.49, 163.02; FABMS *m/z* calcd for $C_{30}H_{31}N_2O_{10}S_2$ (M + H) 643.1412, found 643.1401.

(b) Large scale

$MeSO_2Cl$ (3.78 mL, 48.9 mmol) in dry CH_2Cl_2 (15 mL) was added dropwise to a stirred and cooled (0 °C) solution of 5'-*O*-(triphenylmethyl)uridine (**39**) (5.944 g, 12.22 mmol) and dry pyridine (7.9 mL, 98 mmol) in dry CH_2Cl_2 (25 mL) (Ar atmosphere). The ice bath was removed and stirring was continued for 15 h. The mixture was poured onto ice (*ca.* 200 g) and extracted with EtOAc (2 x 200 mL). The organic extract was washed with water (2 x 100 mL), aqueous NaOH (0.5 M, 2 x 100 mL), and aqueous $CuSO_4$ (10%, 1 x 200 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue twice over silica gel (5 x 35 cm), using 2:98 MeOH-CH_2Cl_2 for the first chromatography, and 1:99 MeOH-CH_2Cl_2 for the second,

gave **40** (5.837 g, 74%) as a pure (^{1}H NMR, 400 MHz), colorless oil, spectroscopically identical to a reference sample.

5-Methyl-5'-*O*-(triphenylmethyl)uridine 2',3'-dimethanesulfonate (44).[110]

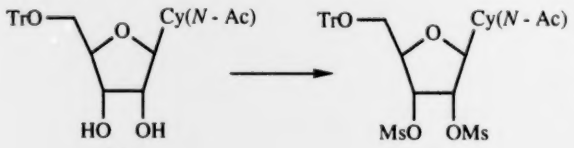


The following procedure differs from the reported one.[110]

$MeSO_2Cl$ (0.11 mL, 1.4 mmol) in CH_2Cl_2 (1 mL) was added dropwise to a stirred and cooled (0 °C) solution of 5-methyl-5'-*O*-(triphenylmethyl)uridine (**43**) (174 mg, 0.348 mmol) and pyridine (0.46 mL, 5.6 mmol) in CH_2Cl_2 (3 mL) (Ar atmosphere). The ice bath was removed and stirring was continued for 48 h. The mixture was poured onto ice (*ca.* 50 g) and extracted with EtOAc (2 x 50 mL). The organic extract was washed with water (2 x 50 mL), aqueous NaOH (0.1 M, 1 x 50 mL), and aqueous $CuSO_4$ (10%), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 x 30 cm), using 3:97 MeOH-CH_2Cl_2, gave pure (^{1}H NMR, 200 MHz) **44** (0.190 g, 83%): FTIR (CH_2Cl_2, cast) 1693, 1364, 1180 cm^{-1}; ^{1}H NMR identical to that reported;[110] ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 11.75, 38.68, 38.84, 61.92, 74.96, 77.24, 81.48, 87.83, 88.23, 112.38, 127.71, 128.22, 128.77, 135.31, 142.92,

150.64, 163.39; FABMS *m/z* calcd for $C_{31}H_{33}N_2O_{10}S_2$ (M + H) 657.1578, found 657.1548.

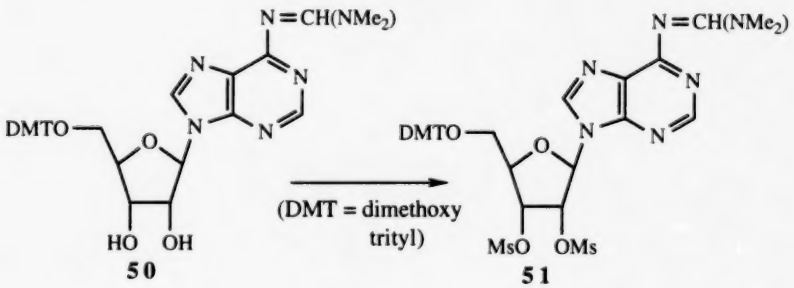
_N_-Acetyl-5'-_O_-(triphenylmethyl)cytidine 2',3'-dimethanesulfonate (48).



$MeSO_2Cl$ (0.061 mL, 0.786 mmol) in CH_2Cl_2 (0.6 mL) was added dropwise to a stirred and cooled (0 °C) solution of *N*-acetyl-5'-*O*-(triphenylmethyl)cytidine (**47**) (0.104 g, 0.196 mmol) and Et_3N (0.060 mL, 0.434 mmol) in CH_2Cl_2 (1 mL) (Ar atmosphere). The mixture was stirred at 0 °C for 25 min, poured onto ice (*ca.* 100 g), and extracted with CH_2Cl_2 (100 mL). The organic extract was washed with water (1 x 100 mL), saturated aqueous $NaHCO_3$ (1 x 100 mL), and water (1 x 100 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1 x 30 cm), using 3.5:96.5 MeOH-CH_2Cl_2, gave pure (^1H NMR, 200 MHz) **48** (0.108 g, 81%): FTIR (CH_2Cl_2, cast) 1722, 1666, 1490, 1366, 1181 cm^{-1}; ^1H NMR (CD_2Cl_2, 200 MHz) δ 2.18 (s, 3 H), 3.06 (s, 3 H), 3.35 (s, 3 H), 3.56 (dd, *J* = 11.5, 2.2 Hz, 1 H), 3.68 (dd, *J* = 11.5, 2.2 Hz, 1 H), 4.30-4.50 (m, 1 H), 5.37-5.55 (m, 2 H), 5.97 (s, br, 1 H), 7.10 (d, *J* = 7.0 Hz, 1 H), 7.20-7.60 (m, 15 H), 8.25 (d, *J* = 7.0 Hz, 1 H), 8.90 (br s, 1 H); ^{13}C NMR (CD_2Cl_2,

100.6 MHz) δ 25.01, 38.90, 39.24, 60.49, 72.58, 79.89, 80.58, 88.22, 90.44, 97.46, 127.87, 128.47, 129.02, 143.30, 144.85, 155.29, 163.71, 171.23; FABMS *m/z* calcd for $C_{32}H_{34}N_3O_{10}S_2$ (M + H) 684.1687, found 684.1651.

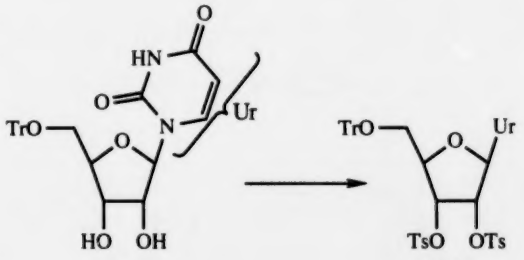
_N_-[(Dimethylamino)methylene]-5'-_O_-[bis(4-methoxyphenyl)phenylmethyl]adenosine 2',3'-dimethanesulfonate (51).



$MeSO_2Cl$ (0.37 mL, 4.8 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a stirred and cooled (0 °C) solution of *N*-[(dimethylamino)methylene]-5'-*O*-[bis(4-methoxyphenyl)phenylmethyl]adenosine (**50**),[54,111] (1.001 g, 1.602 mmol) and Et_3N (1.34 mL, 9.61 mmol) in CH_2Cl_2 (8 mL) (Ar atmosphere). The mixture was stirred at 0 °C for 30 min, poured onto ice (*ca.* 200 g), and extracted with CH_2Cl_2 (2 x 150 mL). The organic extract was washed with water (1 x 100 mL), saturated aqueous $NaHCO_3$ (1 x 100 mL), and water (1 x 100 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 x 30 cm), using 49:30:20:1 CH_2Cl_2-PhMe-MeCN-Et_3N, gave pure (^1H NMR, 200 MHz) **51** (1.089 g, 87%): FTIR

(CH_2Cl_2, cast) 1365, 1180 cm^{-1}; ^1H NMR (acetone-d_6, 200 MHz) δ 3.10-3.30 (m, 12 H), 3.40 (dd, *J* = 11.0, 4.0 Hz, 1 H), 3.62 (dd, *J* = 11.0, 3.5 Hz, 1 H), 3.75 (s, 3 H), 3.76 (s, 3 H), 4.40-4.60 (m, 1 H), 5.85-6.00 (m, 1 H), 6.30-6.55 (m, 2 H), 6.70-6.90 (m, 4 H), 7.10-7.38 (m, 7 H), 7.38-7.55 (m, 2 H), 8.30 (s, 1 H), 8.31 (s, 1 H), 8.85-9.00 (br s, 1 H); ^{13}C NMR (acetone-d_6, 50.3 MHz) δ 35.02, 38.74, 38.80, 41.13, 55.60 (two overlapping signals), 62.99, 77.08, 77.47, 82.51, 87.67, 87.86, 114.06, 127.68, 128.63, 129.14, 131.04, 136.53, 136.65, 145.76, 152.45, 153.25, 159.14, 159.82, 161.16; FABMS *m/z* calcd for ($C_{36}H_{40}N_6O_{10}S_2$ + H) 781.2328, found, 781.2337.

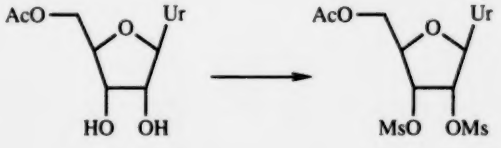
5'-*O*-(Triphenylmethyl)uridine 2',3'-bis(4-methylbenzenesulfonate) (53).



p-Toluenesulfonyl chloride (470 mg, 1.47 mmol) in CH_2Cl_2 (2 mL) was added dropwise to a stirred and cooled (0 °C) solution of 5'-*O*-(triphenylmethyl)uridine **39**[105] (200 mg, 0.411 mmol), pyridine (0.80 mL, 9.9 mmol) and 4-(dimethylamino)pyridine (5 mg) in CH_2Cl_2 (2 mL) (Ar atmosphere). The ice bath was removed, stirring was continued for 24 h, and

the mixture was then heated at 50 °C for a further 24 h. The mixture was poured onto ice (*ca.* 25 g) and extracted with CH_2Cl_2 (1 x 100 mL). The organic extract was washed with aqueous $CuSO_4$ (10%, 2 x 50 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1 x 30 cm), using 55:25:20 CH_2Cl_2-PhMe-MeCN, gave **53** (93 mg, 29%) as a pure (^{1}H NMR, 200 MHz), colorless oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.40 (s, 3 H), 2.45 (s, 3 H), 3.30-3.50 (m, 2 H), 4.30-4.45 (m, 1 H), 5.00-5.35 (m, 3 H), 6.10 (d, *J* = 6.0 Hz, 1 H), 7.15-7.45 (m, 20 H), 7.64 (d, *J* = 8.0 Hz, 2 H), 7.77 (d, *J* = 8.0 Hz, 2 H), 7.96 (br s, 1 H).

5'-*O*-Acetyluridine 2',3'-dimethanesulfonate (57).

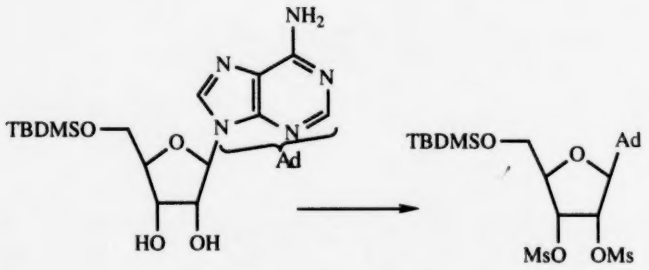


56 **57**

$MeSO_2Cl$ (0.90 mL, 11 mmol) in CH_2Cl_2 (1.6 mL) was added dropwise to a stirred and cooled (ice bath) solution of 5'-*O*-acetyluridine (**56**) (0.332 g, 1.16 mmol) and pyridine (1.50 mL, 18.5 mmol) in CH_2Cl_2 (3 mL) (Ar atmosphere). The ice bath was removed and stirring was continued for 24 h. The mixture was evaporated at room temperature, and flash chromatography of the residue over silica gel (3.5 x 30 cm), using 3:97 MeOH-CH_2Cl_2, gave, after a second chromatography under the same conditions, pure (^{1}H NMR, 200 MHz) **57** (0.417 g, 81%):

FTIR (MeOH, cast) 1365, 1180 cm^{-1}; ^1H NMR (acetone-d_6, 200 MHz) δ 2.07 (s, 3 H), 3.26 (s, 3 H), 3.32 (s, 3 H), 4.30-4.60 (m, 3 H), 5.48 (t, J = 6.0 Hz, 1 H), 5.55-5.80 (m, 2 H), 6.00 (d, J = 3.0 Hz, 1 H), 7.76 (d, J = 8.0 Hz, 1 H), 10.23 (br s, 1 H); ^{13}C NMR (acetone-d_6, 50.3 MHz) δ 20.61, 38.66, 38.74, 62.58, 75.14, 78.61, 80.24, 91.11, 103.34, 141.93, 151.33, 163.36, 170.57; FABMS m/z calcd for ($C_{13}H_{18}N_2O_{11}S_2$ + H) 443.0431, found 443.0398.

5'-*O*-[(1,1-Dimethylethyl)dimethylsilyl]adenosine 2',3'-dimethanesulfonate (60).



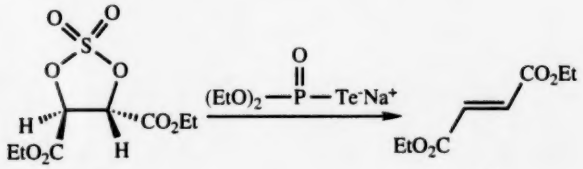
59 **60**

$MeSO_2Cl$ (0.57 mL, 7.3 mmol) in CH_2Cl_2 (2 mL) was added dropwise to a stirred and cooled (0 °C) solution of **59**[112] (0.700 g, 1.84 mmol) in a mixture of CH_2Cl_2 (2 mL) and pyridine (8.3 mL). After 1 h, the ice bath was removed and stirring was continued for 24 h, the mixture was then poured onto ice, EtOAc (200 mL) was added, and the organic layer was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 × 20 cm), using 5:95 MeOH-CH_2Cl_2,

gave **60** (0.773 g, 78%) as a pure (^{1}H NMR, 200 MHz), colorless oil: FTIR (CH_2Cl_2, cast) 3315, 3148 cm^{-1}; ^{1}H NMR (acetone-d_6, 200 MHz) δ 0.07 (s, 3 H), 0.90 (s, 3 H), 0.88 (s, 9 H), 3.25 (s, 3 H), 3.32 (s, 3 H), 3.92-4.02 (dd, J = 12, 4 Hz, 1 H), 4.02-4.15 (dd, J = 12, 4 Hz, 1 H), 4.38-4.48 (m, 1 H), 5.70-5.80 (ap t, J = 5 Hz, 1 H), 6.08-6.18 (ap t, J = 5 Hz, 1 H), 6.32-6.38 (d, J = 5 Hz, 1 H), 6.60-6.76 (br s, 2 H), 8.22 (s, 1 H), 8.25 (s, 1 H); ^{13}C NMR (acetone-d_6, 50.3 MHz) δ -5.40 (two overlapping signals), 18.94, 26.28 (three overlapping signals), 38.67 (two overlapping signals), 62.29, 76.20, 78.31, 83.50, 87.15, 120.89, 140.49, 150.50, 153.96, 157.36; FABMS *m/z* calcd for $C_{18}H_{32}N_5O_8S_2Si$ (M + H) 538, found 538.

Deoxygenation experiments

Diethyl fumarate (21).[99]

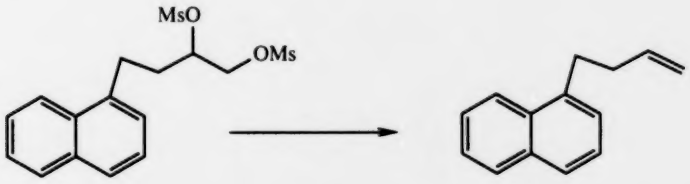


20 **21**

$(EtO)_2P(O)Na$[47] (0.65 M in EtOH, 0.65 mL, 0.43 mmol) was added to Te powder (200 mesh, 0.036 g, 0.289 mmol) and the mixture was stirred for 1.5 h. After the Te had dissolved, cyclic sulfate **20**[48] (0.077 g, 0.288 mmol) in deoxygenated EtOH[113] (2 mL) was added. Stirring was continued for 12 h and

then hexane (20 mL) was added. The organic layer was washed with water (3 × 20 mL), dried ($MgSO_4$), filtered through Celite, and evaporated to afford diethyl fumarate (**21**)[99] (0.018 g, 36%) as a pure (^1H NMR, 200 MHz), colorless oil: ^1H NMR ($CDCl_3$, 200 MHz) δ 1.33 (ap t, J = 8 Hz, 6 H), 4.28 (ap q, J = 8 Hz, 4 H), 6.86 (ap s, 2 H).

1-(3-Butenyl)naphthalene (24).



26 **24**

(a) Use of Li_2Te

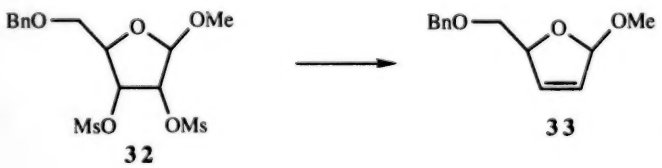
Te powder (200 mesh, 0.167 g, 1.31 mmol) and a small stirring bar were placed in a dry round-bottomed flask fused onto a reflux condenser. The flask was closed with a septum and flushed with Ar. A solution of Et_3BHLi (1 M in THF, 3.4 mL, 3.4 mmol) was injected, and the mixture was stirred until a milky white suspension had formed (*ca.* 5 h). 4-(1-Naphthyl)butane-1,2-diol dimethanesulfonate (**26**) (488 mg, 1.31 mmol) in THF (5 mL) was then injected dropwise and the mixture was stirred for 20 h. The mixture was washed out of the flask with acetone and evaporated at room temperature. Flash chromatography of the residue over silica gel (2 x 30

cm), using hexane, gave pure (tlc, silica, hexane) **24** (210 mg, 88%), spectroscopically identical to a known sample.

(b) Use of $(EtO)_2P(O)Na$

$(EtO)_2P(O)Na$[47] (0.65 M in EtOH, 0.95 mL, 0.60 mmol) was added to Te powder (0.071 g, 200 mesh, 0.559 mmol) and the mixture was stirred at room temperature for 1 h, by which stage all the Te had dissolved. Dimesylate **26** (0.099 g, 0.266 mmol) in absolute EtOH (2 mL) and THF (0.5 mL) was added. The mixture was stirred at room temperature for 24 h and then heated at 80 °C for 1 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 × 20 cm), using hexane, gave **24** (0.016 g, 33%) as a pure (^1H NMR, 200 MHz), colorless oil, spectroscopically identical to a known sample.

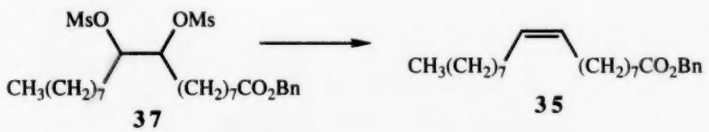
Methyl 5-*O*-benzyl-2,3-dideoxy-β-D-pent-2-enofuranoside (33).[114]



Te powder (200 mesh, 72 mg, 0.565 mmol) and a small stirring bar were placed in a dry round-bottomed flask fused onto a reflux condenser. The flask was closed with a septum and flushed with Ar. A solution of Et_3BHLi (1 M in THF, 1.27

mL, 1.27 mmol) was injected and the mixture was stirred until a milky white suspension had formed (*ca.* 5 h). Methyl 5-*O*-benzyl-2,3-di-*O*-mesyl-β-D-ribofuranoside (**32**) (100 mg, 0.244 mmol) in dioxane (5 mL) was then injected dropwise and the mixture was refluxed for 20 h. At this stage all of the dimesylate had reacted (tlc, silica, 30:70 EtOAc-hexane). The mixture was cooled, washed out of the flask with acetone, and evaporated at room temperature. Flash chromatography of the residue over silica gel (1 x 20 cm), using 1:9 EtOAc-hexane, gave **33** (37 mg, 69%) as a pure (^{1}H NMR, 200 MHz), colorless oil: FTIR (neat film) unexceptional; ^{1}H NMR identical to that reported;[114] ^{13}C NMR (acetone-d_6, 75.5 MHz) δ 54.25, 73.54, 74.38, 85.31, 110.06, 128.11, 128.24, 128.33, 128.97, 133.74, 139.66; CIMS *m/z* calcd for $C_{13}H_{16}O_3$ 220, found 220.

Oleic acid benzyl ester (35).[104]



(a) Use of Li_2Te.

Te powder (200 mesh, 53 mg, 0.412 mmol) and a small stirring bar were placed in a dry round-bottomed flask fused onto a reflux condenser. The flask was closed with a septum and flushed with Ar. A solution of Et_3BHLi (1 M in THF, 0.78 mL, 0.78 mmol) was injected and the mixture was stirred until

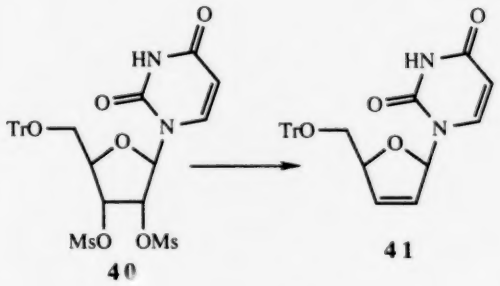
a milky white suspension had formed (*ca.* 5 h). Dimesylate **37** (108 mg, 0.192 mmol) in dioxane (5 mL) was then injected dropwise and the mixture was stirred for 14 h. Starting material (tlc, silica, 40:60 CH_2Cl_2-hexane) was still present and so the mixture was heated at 100 °C for 2 h (tlc control). The mixture was cooled, washed out of the flask with hexane, and evaporated at room temperature. Flash chromatography of the residue over silica gel (1.5 x 20 cm), using 40:60 CH_2Cl_2-hexane, gave **35** (59 mg, 83%) as a pure (^1H NMR, 200 MHz), colorless oil, spectroscopically identical to a known sample.

(b) Use of Li_2Se.

Se powder (325 mesh, 29 mg, 0.360 mmol) and a small stirring bar were placed in a dry round-bottomed flask fused onto a reflux condenser. The flask was closed with a septum and flushed with Ar. A solution of Et_3BHLi (1 M in THF, 0.68 mL, 0.68 mmol) was injected and the mixture was stirred until a milky white suspension had formed (*ca.* 20 min). Dimesylate **37** (101 mg, 0.179 mmol) in dioxane (5 mL) was then injected dropwise and the mixture was stirred for 24 h. Starting material was still present (tlc, silica gel, 40:60 CH_2Cl_2-hexane), and the mixture was therefore heated at 100 °C for 4 h. The mixture was cooled, washed out of the flask with hexane, and evaporated at room temperature. Flash chromatography of the residue over silica gel (1 x 30 cm), using 35:65 CH_2Cl_2-hexane, gave **35** (50.8 mg, 76%) as a pure

(^{1}H NMR, 200 MHz), colorless oil, spectroscopically identical to a known sample.

2',3'-Didehydro-2',3'-dideoxy-5'-*O*-(triphenylmethyl)-uridine (41).[15]



(a) Use of Li_2Te on a small scale

Te powder (200 mesh, 40 mg, 0.313 mmol) and a small stirring bar were placed in a dry round-bottomed flask fused onto a reflux condenser. The flask was closed with a septum and flushed with Ar. A solution of Et_3BHLi (1 M in THF, 0.66 mL, 0.66 mmol) was injected and the mixture was stirred until a milky white suspension had formed (*ca.* 5 h). Dimesylate **40** (100 mg, 0.155 mmol) in dioxane (5 mL) was then injected dropwise and the mixture was stirred for 48 h. The mixture was washed out of the flask with CH_2Cl_2, and evaporated at room temperature. Flash chromatography of the residue over silica gel (2 x 25 cm), using 50:35:15 CH_2Cl_2-PhMe-MeCN, gave **41** (56 mg, 80%) as a pure (^{1}H NMR, 200 MHz), colorless oil, spectroscopically identical to a known[15] sample.

(b) Use of Li_2Te in the presence of MeCN

Te powder (200 mesh, 42 mg, 0.327 mmol) and a small stirring bar were placed in a dry round-bottomed flask fused onto a reflux condenser. The flask was closed with a septum and flushed with Ar. A solution of Et_3BHLi (1 M in THF, 0.73 mL, 0.73 mmol) was injected and the mixture was stirred until a milky white suspension had formed (*ca.* 5 h). Dimesylate **40** (100 mg, 0.155 mmol) in MeCN (2 mL) was then injected dropwise and the mixture was stirred for 16 h. The mixture was washed out of the flask with CH_2Cl_2 and evaporated at room temperature. Flash chromatography of the residue over silica gel (1 x 30 cm), using 55:25:20 CH_2Cl_2-PhMe-MeCN, gave **41** (70 mg, 99%) as a pure (^1H NMR, 200 MHz), colorless oil, spectroscopically identical to a known[15] sample.

(c) Use of Na_2Te in the presence of MeCN.

Dimesylate **40** (1.287 g, 2.003 mmol) in MeCN (40 mL), was added to Na_2Te (0.869 g, 5.01 mmol, weighed out in a glove bag) and the mixture was stirred at room temperature for 24 h. Evaporation of the solvents and flash chromatography of the residue over silica gel (4 × 20 cm), using 5.5:2.5:2 CH_2Cl_2-PhMe-MeCN, gave **41** (0.400 g, 44%) as a pure (^1H NMR, 200 MHz), colorless oil, spectroscopically identical to a known[15] sample.

(d) Use of Na_2Te on a small scale.

Na_2Te (0.094 g, 0.541 mmol) (prepared from the elements, as described above) and a small stirring bar were placed in a dry round-bottomed flask fused onto a reflux condenser. The flask was closed with a septum and flushed with Ar. Dimesylate **40** (139 mg, 0.216 mmol) in THF (2 mL) was then injected and the mixture was stirred for 20 h at room temperature. The mixture was washed out of the flask with CH_2Cl_2, and evaporated at room temperature. Flash chromatography of the residue over silica gel (1 x 25 cm), using 55:25:20 CH_2Cl_2-PhMe-MeCN, gave **41** (91 mg, 93%) as a pure (^1H NMR, 200 MHz), colorless oil, spectroscopically identical to a known[15] sample.

(e) Use of Na_2Te on a large scale.

Na_2Te (1.796 g, 10.35 mmol) (prepared from the elements, as described above) and a small stirring bar were placed in a dry 100-mL round-bottomed flask closed with a septum. The flask was flushed with Ar. Dimesylate **40** (2.660 g, 4.139 mmol) in dry THF (40 mL) was then injected and the mixture was stirred for 20 h at room temperature. The mixture was washed out of the flask with CH_2Cl_2, and evaporated at room temperature. Flash chromatography of the residue over silica gel (4 x 30 cm), using 55:25:20 CH_2Cl_2-PhMe-MeCN, gave **41** (1.402 g, 75%) as a pure (^1H NMR, 400 MHz), colorless oil, spectroscopically identical to a known[15] sample.

(f) Use of Li_2Se

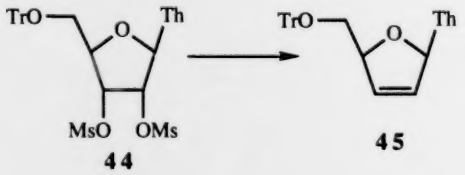
Se powder (325 mesh, 15 mg, 0.187 mmol) and a small stirring bar were placed in a dry round-bottomed flask fused onto a reflux condenser. The flask was closed with a septum and flushed with Ar. A solution of Et_3BHLi (1 M in THF, 0.37 mL, 0.37 mmol) was injected and the mixture was stirred for *ca.* 4 h. A milky white suspension was formed after 10 min. Dimesylate **40** (59 mg, 0.093 mmol) in THF (3 mL) was then injected dropwise and the mixture was stirred for 20 h. The mixture turned brown on initial addition of the dimesylate solution. The mixture was washed out of the flask with CH_2Cl_2, K_2CO_3 (0.5 g) was added, and the mixture was then evaporated at room temperature. Flash chromatography of the residue over silica gel (1 x 20 cm), using 50:35:15 CH_2Cl_2-PhMe-MeCN, gave **41** (27 mg, 65%) as a pure (^1H NMR, 200 MHz), colorless oil, spectroscopically identical to a known[15] sample.

(g) Use of Na_2Se

Na_2Se (0.030 g, 0.241 mmol) (prepared from the elements, as described above) and a small stirring bar were placed in a dry round-bottomed flask fused onto a reflux condenser. The flask was closed with a septum and flushed with Ar. Dimesylate **40** (59 mg, 0.092 mmol) in THF (2 mL) was then injected and the mixture was stirred for 48 h. The mixture was washed out of the flask with CH_2Cl_2 and evaporated at room temperature. Flash chromatography of the residue twice over

silica gel (1 x 25 cm), using 55:25:20 CH_2Cl_2-PhMe-MeCN, gave **41** (21.3 mg, 51%) as a pure (^{1}H NMR, 200 MHz), colorless oil, spectroscopically identical to a known[15] sample.

2',3'-Didehydro-2',3'-dideoxy-5-methyl-5'-*O*-(triphenylmethyl)uridine (45).[115]

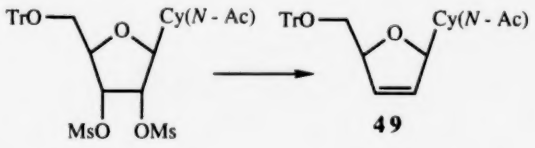


44 **45**

Te powder (200 mesh, 25 mg, 0.195 mmol) and a small stirring bar were placed in a dry round-bottomed flask fused onto a reflux condenser. The flask was closed with a septum and flushed with Ar. A solution of Et_3BHLi (1 M in THF, 0.50 mL, 0.50 mmol) was injected and the mixture was stirred until a milky white suspension had formed (*ca.* 5 h). Dimesylate **44** (60 mg, 0.092 mmol) in THF (3 mL) was then injected dropwise and the mixture was stirred for 48 h. The mixture was washed out of the flask with CH_2Cl_2 and evaporated at room temperature. Flash chromatography of the residue over silica gel (2 x 30 cm), using 50:35:15 CH_2Cl_2-PhMe-MeCN, gave pure (^{1}H NMR, 200 MHz) **45** (38.6 mg, 90%): FTIR (CH_2Cl_2, cast) 1689 cm^{-1}; ^{1}H NMR identical to that reported;[115] ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 11.40, 64.96, 85.72, 87.03, 89.71, 111.28, 126.35, 127.41,* 127.97,* 128.79,* 134.56, 136.03, 143.25,* 150.80, 163.82 (the four starred signals represent

18 carbons in trityl group); exact mass *m/z* calcd for $C_{20}H_{17}O$ (M - $C_9H_9N_2O_3$) 273.1279, found 273.1281; exact mass *m/z* calcd for $C_9H_9N_2O_3$ (M - $C_{20}H_{17}O$) 193.0613, found 193.0611.

N-Acetyl-2',3'-didehydro-2',3'-dideoxy-5'-O-(triphenylmethyl)cytidine (49).



48 49

(a) Use of Li_2Te

Te powder (200 mesh, 39 mg, 0.307 mmol) and a small stirring bar were placed in a dry round-bottomed flask fused onto a reflux condenser. The flask was closed with a septum and flushed with Ar. A solution of Et_3BHLi (1 M in THF, 0.66 mL, 0.66 mmol) was injected and the mixture was stirred until a milky white suspension had formed (*ca.* 5 h). Dimesylate **48** (100 mg, 0.146 mmol) in THF (2 mL) was then injected dropwise and the mixture was stirred for 14 h. The mixture was washed out of the flask with CH_2Cl_2, and evaporated at room temperature. Flash chromatography of the residue over silica gel (1 x 15 cm), using 50:30:20 MeCN-CH_2Cl_2-PhMe, gave **49** (60 mg, 83%) as a colorless oil containing trace impurities (^1H NMR, 200 MHz): FTIR (CH_2Cl_2, cast) 1722, 1672 cm^{-1}; ^1H NMR (CD_2Cl_2, 200 MHz) δ 2.18 (s, 3 H), 3.30-3.50 (m, 2 H), 4.95-5.15 (m, 1 H), 5.93-6.08 (m, 1 H), 6.18-6.43 (m, 1 H), 6.87

(d, J = 7.0 Hz, 1 H), 6.92-7.05 (m, 1 H), 7.15-7.55 (m, 15 H), 8.0 (d, J = 7.0 Hz, 1 H), 8.92 (br s, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 25.04, 65.21, 86.84, 87.61, 92.00, 96.77, 127.42, 127.68,* 128.34,* 129.04,* 133.71, 143.78,* 145.70, 155.80, 163.30, 171.03 (the four starred signals represent 18 carbons in trityl group); exact mass m/z calcd for $C_{19}H_{15}$ (M - $C_{11}H_{12}N_3O_4$) 243.1174, found 243.1173; exact mass m/z calcd for $C_{11}H_{12}N_3O_4$ (M - $C_{19}H_{15}$) 250.0828, found 250.0836.

(b) Use of Na_2Te

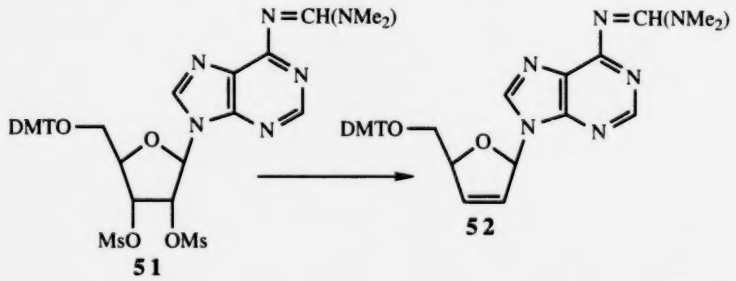
Na_2Te (0.068 g, 0.393 mmol) (prepared from the elements, as described above) and a small stirring bar were placed in a dry round-bottomed flask fused onto a reflux condenser. The flask was closed with a septum and flushed with Ar. The dimesylate **48** (107 mg, 0.157 mmol) in THF (2 mL) was then injected and the mixture was stirred for 24 h. The mixture was washed out of the flask with CH_2Cl_2, and evaporated at room temperature. Flash chromatography of the residue over silica gel (1 x 25 cm), using 50:30:20 MeCN-CH_2Cl_2-PhMe, gave **49** (33 mg, 42%) as a pure (^1H NMR, 400 MHz), colorless oil, spectroscopically identical to a known sample.

_N_-Acetyl-2',3'-dideoxy-5'-_O_-(triphenylmethyl)cytidine (94).

49 **94**

_N_-Acetyl-2',3'-didehydro-2',3'-dideoxy-5'-_O_-(triphenylmethyl)cytidine (**49**) (50 mg, 0.101 mmol), EtOAc (3 mL) and MeOH (1 mL) were placed in a test tube together with Pd/charcoal (10%w/w, 10 mg). The test tube was supported with glass wool in a Parr vessel and shaken with hydrogen (50 psi) for 4 h. The mixture was filtered and evaporated. Flash chromatography of the residue over silica gel (1 cm x 30 cm), using 50:30:20 MeCN-CH_2Cl_2-PhMe, gave **94** (30 mg, 61%) as a pure (^{1}H NMR, 200 MHz), colorless oil: ^{1}H NMR (CD_2Cl_2, 200 MHz) δ 1.82-2.03 (m, 1 H), 2.20 (s, 3 H), 2.35-2.63 (m, 1 H), 3.28-3.58 (m, 2 H), 4.17-4.38 (m, 1 H), 5.95-6.10 (m, 1 H), 7.12 (d, J = 7.0 Hz, 2 H), 7.20-7.60 (m, 15 H), 8.32 (d, J = 7.0 Hz, 2 H), 9.68 (br s, 1 H).

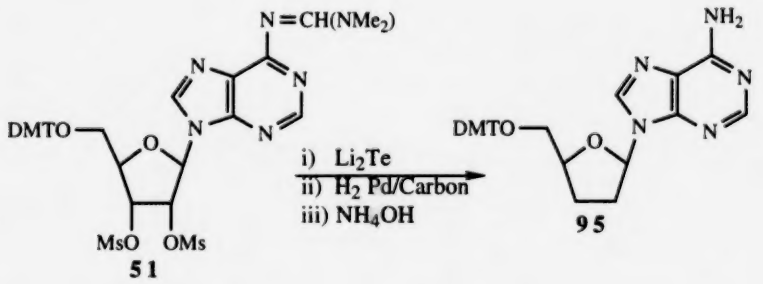
2',3'-Didehydro-2',3'-dideoxy-*N*-[(dimethylamino)-methylene]-5'-*O*-[bis(4-methoxyphenyl)phenylmethyl]-adenosine (52).



Te powder (200 mesh, 20 mg, 0.156 mmol) and a small stirring bar were placed in a dry round-bottomed flask fused onto a reflux condenser. The flask was closed with a septum and flushed with Ar. A solution of Et_3BHLi (1 M in THF, 0.33 mL, 0.33 mmol) was injected and the mixture was stirred until a milky white suspension had formed (*ca.* 5 h). Dimesylate **51** (58 mg, 0.074 mmol) in THF (2 mL) was then injected dropwise and the mixture was stirred for 16 h. The mixture was washed out of the flask with CH_2Cl_2, and evaporated at room temperature. Flash chromatography of the residue over silica gel (1 x 30 cm), using 29:20:50:1 CH_2Cl_2-PhMe-MeCN-Et_3N, gave **52** (39 mg, *ca.* 89%), containing trace impurities (^1H NMR, 200 MHz): ^1H NMR (acetone-d_6, 200 MHz) δ 3.02-3.30 (m, 6 H), 3.30-3.46 (m, 1 H), 3.46-3.65 (m, 1 H), 3.74 (s, 3 H), 3.75 (s, 3 H), 5.02-5.18 (m, 1 H), 6.15-6.30 (m, 1 H), 6.48-6.60 (m, 1 H), 6.60-6.90 (m, 4 H), 7.00-7.32 (m, 8 H), 7.32-7.50 (m, 2 H), 8.01 (s, 1 H), 8.42 (s, 1 H), 8.86-9.05 (s, 1 H).

For characterization the material was processed as described in the next experiment.

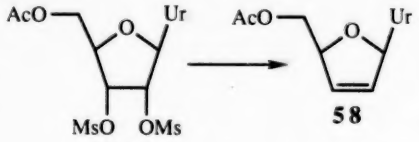
5'-*O*-[Bis(4-methoxyphenyl)phenylmethyl]-2',3'-dideoxy-adenosine. (95).[116]



Te powder (200 mesh, 34 mg, 0.270 mmol) and a small stirring bar were placed in a dry round-bottomed flask fused onto a reflux condenser. The flask was closed with a septum and flushed with Ar. A solution of Et_3BHLi (1 M in THF, 0.60 mL, 0.60 mmol) was injected and the mixture was stirred at 40 °C for 0.5 h, by which time the solution had turned white. Dimesylate **51** (0.100 g, 0.128 mmol) in THF (2 mL) was added to the resulting Li_2Te suspension. The mixture was stirred at room temperature for 14 h and then β-cyclodextrin (0.5 g) was added together with 5:2.9:2:0.1 MeCN-CH_2Cl_2-PhMe-Et_3N (20 mL). The resulting mixture was evaporated to deposit the Te on the β-cyclodextrin, and then filtered through β-cyclodextrin (3 x 3 cm), using the above solvent system. Silica (1 g) was added to the filtrate and the mixture was evaporated. MeOH (20 mL) was added and the mixture was again

filtered, using MeOH. The filtrate was evaporated and MeOH (4 mL) was added together with Pd/carbon (0.02 g). The mixture was placed under H_2 (50 psi) and shaken for 3 h. The mixture was filtered and a ^1H NMR spectrum was taken to determine if hydrogenation was complete. MeOH (4 mL) and Pd/carbon (0.02 g) were again added and the reaction was set up as before and continued for 12 h. At this stage hydrogenation was complete (^1H NMR). THF (4 mL) and concentrated NH_4OH (0.4 mL) were added and the mixture was stirred for 1 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 × 15 cm), using 5:2.9:2:0.1 MeCN-CH_2Cl_2-PhMe-Et_3N, gave **95** (0.030 g, 43%) as a pure (^1H NMR, 200 MHz), colorless oil: FTIR (CH_2Cl_2, cast) 3320, 3180 cm^{-1}; ^1H NMR (acetone-d_6, 200 MHz) δ 2.10-2.35 (m, 2 H), 2.45-2.75 (m, 2 H), 3.22-3.38 (m, 2 H), 3.75 (s, 6 H), 4.28-4.44 (m, 1 H), 6.28-6.38 (m, 1 H), 6.65-6.88 (m, 6 H), 7.10-7.48 (m, 9 H), 8.15 (s, 1 H), 8.19 (s, 1 H); ^{13}C NMR (acetone-d_6, 50.3 MHz) δ 27.54, 32.51, 55.52, 66.50, 81.44, 86.07, 86.44, 113.88, 127.48, 128.51, 129.07, 130.92, 137.00 (two overlapping signals), 146.23, 150.46, 153.50 (two overlapping signals), 157.06, 159.64; exact mass *m/z* calcd for $C_{31}H_{31}N_5O_4$ 537.2376, found 537.2374.

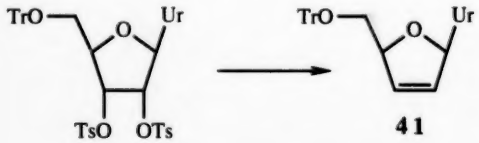
5'-*O*-Acetyl-2',3'-didehydro-2',3'-dideoxyuridine (58).[15]



57 58

Te powder (200 mesh, 61 mg, 0.475 mmol) and a small stirring bar were placed in a dry round-bottomed flask fused onto a reflux condenser. The flask was closed with a septum and flushed with Ar. A solution of Et_3BHLi (1 M in THF, 1.17 mL, 1.17 mmol) was injected and the mixture was stirred until a milky white suspension had formed (*ca.* 5 h). Dimesylate **57** (100 mg, 0.226 mmol) in THF (3 mL) was then injected dropwise and the mixture was stirred for 96 h. The mixture was washed out of the flask with CH_2Cl_2 and evaporated at room temperature. Flash chromatography of the residue over silica gel (1 x 30 cm), using 3:97 MeOH-CH_2Cl_2, gave **58** (7.7 mg, 14%) as a pure (^{1}H NMR, 200 MHz), colorless oil, spectroscopically identical to a known[15] sample.

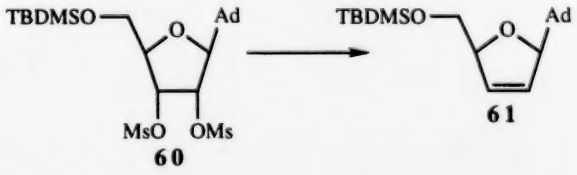
2',3'-Di-dehydro-2',3'-dideoxy-5'-*O*-(triphenylmethyl)-uridine (41).[15]



53 41

Te powder (200 mesh, 12 mg, 0.092 mmol) and a small stirring bar were placed in a dry round-bottomed flask fused onto a reflux condenser. The flask was closed with a septum and flushed with Ar. A solution of Et_3BHLi (1 M in THF, 0.21 mL, 0.21 mmol) was injected and the mixture was stirred until a milky white suspension had formed (*ca.* 5 h). Ditosylate **53** (34.8 mg, 0.0438 mmol) in THF (1 mL) was then injected dropwise and the mixture was stirred for 24 h. The mixture was washed out of the flask with CH_2Cl_2, and evaporated at room temperature. Flash chromatography of the residue over silica gel (1 x 30 cm), using 50:25:20 CH_2Cl_2-PhMe-MeCN, gave **41** (11.8 mg, 60%) as a pure (^1H NMR, 200 MHz), colorless oil, spectroscopically identical to a known[15] sample.

5'-*O*-[(1,1-Dimethylethyl)dimethylsilyl]-2',3'-didehydro-2',3'-dideoxyadenosine (61).[117]



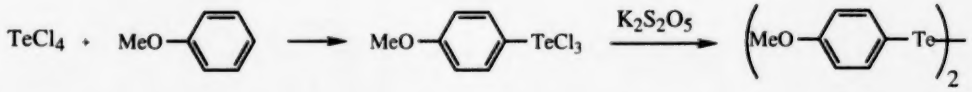
Te powder (200 mesh, 0.113 g, 0.887 mmol) and a small stirring bar were placed in a dry round-bottomed flask fused onto a reflux condenser. The flask was closed with a septum and flushed with Ar. A solution of Et_3BHLi (1 M in THF, 2.0 mL, 2.0 mmol) was injected and the mixture was stirred until

a milky white suspension had formed (*ca.* 6 h). Dimesylate **60** (0.200 g, 0.372 mmol) in THF (2 mL) was then injected dropwise and the mixture was stirred for 20 h. The mixture was washed out of the flask with CH_2Cl_2, and evaporated at room temperature. Flash chromatography of the residue over silica gel (2 x 15 cm), using 5:95 MeOH-CH_2Cl_2, gave **61** (0.101 g, 78%) as a pure (^{1}H NMR, 200 MHz), colorless oil: ^{1}H NMR (acetone-d_6, 200 MHz) δ 0.04 (s, 6 H), 0.88 (s, 9 H), 3.87 (ap d, J = 5 Hz, 2 H), 4.90-5.02 (m, 1 H), 6.12-6.23 (m, 1 H), 6.48-6.55 (m, 1 H), 6.88-7.13 (m, 3 H), 8.15 (s, 1 H), 8.24 (s, 1 H).

Deoxygenations using ditellurides and diselenides

Preparation of reagents

Bis-*p*-anisylditelluride (74).[77]



74

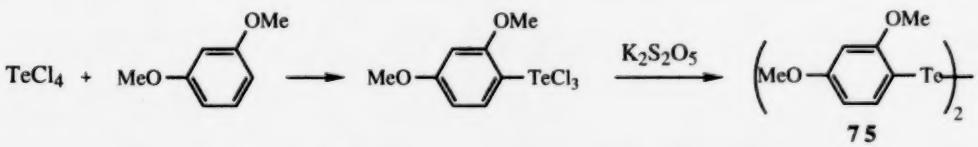
The literature procedure[77] was modified slightly.

Anisole (4.8 mL, 44 mmol) was added to a stirred solution of $TeCl_4$ (3.96 g, 14.7 mmol) in $CHCl_3$ (40 mL). The mixture was refluxed for 1.5 h by which stage a yellow-green precipitate had formed. The mixture was cooled and the precipitate was filtered off and dissolved in boiling $CHCl_3$,

residual insoluble material being removed by filtration. The solution was cooled and the resulting precipitate was collected.

The crude *p*-anisyltelluritrichloride (0.94 g, 2.8 mol) was mixed with water (100 mL) and $K_2S_2O_5$ was added slowly with stirring. The mixture changed from a yellow to a brown-orange suspension. $K_2S_2O_5$ was added until Te started to precipitate. The suspension was filtered, and flash chromatography of the precipitate over silica gel (2 × 20 cm), using 1:24 EtOAc-hexane, gave **74** (0.471 g, 73%) as a pure (^{1}H NMR, 400 MHz), orange solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.78 (s, 6 H), 6.74 (d, *J* = 4 Hz, 4 H), 7.68 (d, *J* = 4 Hz, 4 H).

Bis-[1,3-(dimethoxy)phenyl]-4,4-ditelluride (75).[78]



75

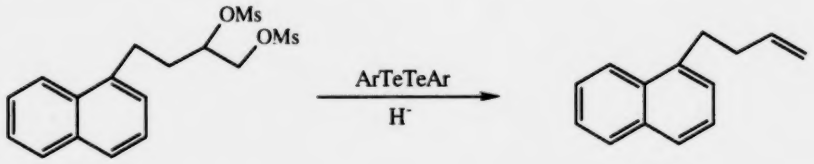
The literature procedure[78] was modified slightly.

1,3-Dimethoxybenzene (2.0 mL, 15 mmol) was added to a stirred solution of $TeCl_4$ (4.19 g, 15.6 mmol) in $CHCl_3$ (40 mL). The mixture was refluxed for 2.5 h, during which time the color changed from orange to dark green. The $CHCl_3$ was evaporated and water (45 mL), EtOAc (100 mL), and $K_2S_2O_5$ (10.4 g) were added. The mixture was shaken, and the organic layer was dried ($MgSO_4$), and evaporated. Flash chromatography of

the residue over silica gel (3 × 15 cm), using PhMe, gave **75** (1.282 g, 31%) as a pure (^{1}H NMR, 200 MHz), orange solid: ^{1}H NMR (acetone-d_6, 200 MHz) δ 3.78 (s, 6 H), 3.88 (s, 6 H), 6.42-6.56 (m, 4 H), 7.45-7.52 (d, J = 8 Hz, 2 H); exact mass m/z calcd for $C_{16}H_{18}O_4{}^{128}Te_2$ 529.9295, found 529.9304, m/z calcd for $C_{16}H_{18}O_4{}^{130}Te_2$ 533.9329, found 533.9335; FABMS m/z calcd for $C_{16}H_{18}O_4{}^{128}Te_2$ 530, found 530.

Deoxygenation experiments

1-(3-Butenyl)naphthalene (24).[98]



26 **24**

(a) $NaBH_4$/EtOH and di(2,4-dimethoxyphenyl)ditelluride (75).

Ditelluride **75** (0.278 g, 0.525 mmol) was placed in a three-neck round-bottomed flask carrying a side arm addition tube containing $NaBH_4$ (0.182 g, 6.88 mmol). Deoxygenated EtOH (5 mL) was added and the mixture was stirred and cooled (0 °C). The $NaBH_4$ was added slowly (H_2 evolution) until the orange solution turned clear. After 1 h the cold bath was removed and stirring was continued for 1 h. Dimesylate **26** (0.163 g, 0.437 mmol) in THF (2 mL) was then added and, after

4 h, CH_2Cl_2 (20 mL) was added and the solution was evaporated. Addition of CH_2Cl_2 and evaporation was repeated twice more and the residue was then adsorbed on silica gel (0.5 g) from a little CH_2Cl_2. Flash chromatography over silica gel (3 × 30 cm), using hexane, gave **24** (0.076 g, 95%) as a pure (^{1}H NMR, 200 MHz), colorless oil, spectroscopically identical to a known sample.

(b) $NaBH_4$/EtOH and a catalytic amount of di(2,4-dimethoxyphenyl)ditelluride (75).

Absolute EtOH (1 mL) was added to ditelluride **75** (0.029 g, 0.056 mmol) in a three-neck round-bottomed flask fitted with a side arm addition tube containing $NaBH_4$ (0.173 g, 4.57 mmol). Dimesylate **26** (0.161 g, 0.432 mmol) in THF (2 mL) was added and then the $NaBH_4$ was added over 5-6 h. The mixture was stirred at room temperature for a further 22 h. CH_2Cl_2 (25 mL) was added and the solvent was evaporated. Addition of CH_2Cl_2 (25 mL) and evaporation was repeated twice more, and the residue was then adsorbed on silica (0.5 g) from a little CH_2Cl_2. Flash chromatography over silica gel (2 × 20 cm), using hexane, gave **24** (0.070 g, 89%) as a pure (^{1}H NMR, 200 MHz), colorless oil, spectroscopically identical to a known sample.

(c) $NaB(OMe)_3H$/DMF and di(2,4-dimethoxyphenyl)-ditelluride (75).

DMF (5 mL) was added to a mixture of solid **75** (0.105 g, 0.281 mmol) and $NaB(OMe)_3H$[99] (0.101 g, 0.786 mmol). The mixture was heated at 60 °C for 1 h, by which time it had become colorless. Dimesylate **26** (0.105 g, 0.281 mmol) in DMF (3 mL) was then added and stirring at room temperature was continued for 1.5 h. Hexane (100 mL) and water (100 mL) were added, the mixture was shaken, and the organic layer was dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using hexane, gave **24** (0.045 g, 88%) as a pure (^1H NMR, 200 MHz), colorless oil, spectroscopically identical to a known sample.

(d) NaH/HMPA/THF and diphenyl diselenide.

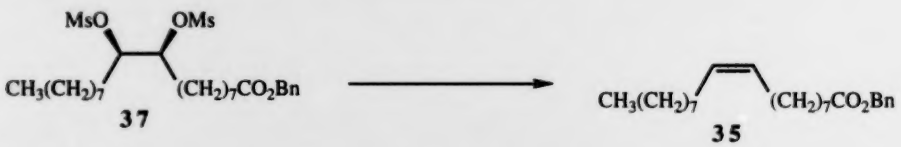
THF (5 mL) was added to a mixture of solid $(PhSe)_2$ (0.113 g, 0.363 mmol) and NaH (0.022 g, 0.727 mmol, 80% dispersion in oil). The mixture was refluxed for 45 min and then HMPA (0.2 mL) was added.[118] The mixture turned orange. Dimesylate **26** (0.113 g, 0.303 mmol) in THF (3 mL) was added and the mixture was stirred at room temperature for 12 h. EtOH (2 mL) was added and $NaBH_4$ (0.12 g) was added to the stirred and cooled (-23 °C) mixture. Bromoacetic acid (0.3 g) was then added and the mixture was stirred at -23 °C for 30 min. The mixture was partitioned between Et_2O (100 mL) and saturated aqueous $NaHCO_3$ (100 mL). The organic layer was washed with water and brine, dried ($MgSO_4$), and evaporated.

Flash chromatography of the residue over silica gel (1 × 20 cm), using hexane, gave **24** (0.049 g, 89%) as a pure (^{1}H NMR, 200 MHz), colorless oil, spectroscopically identical to a known sample.

(e) NaB(OMe)$_3$H/DMF and diphenyl diselenide.

DMF (5 mL) was added to a mixture of solid $(PhSe)_2$ (0.130 g, 0.416 mmol) and $NaB(OMe)_3H$ (0.124 g, 0.971 mmol). The mixture was warmed to 60 °C until it was very pale yellow (45 min). The mixture was cooled to room temperature and dimesylate **26** (0.129 g, 0.347 mmol) in DMF (5 mL) was added. The mixture was stirred at room temperature for 12 h and then partitioned between hexane (100 mL) and water (100 mL). The hexane extract was washed with water and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (1 × 20 cm), using hexane, gave **24** (0.039 g, 61%) as a pure (^{1}H NMR, 200 MHz), colorless oil, spectroscopically identical to a known sample.

Oleic acid benzyl ester (35).



(a) NaH/HMPA/THF and diphenyl diselenide.

THF (5 mL) was added to a mixture of solid $(PhSe)_2$ (0.172 g, 0.550 mmol) and NaH (0.033 g, 1.10 mmol, 80% dispersion in oil). The mixture was refluxed for 45 min and then cooled to room temperature. Dry HMPA (0.2 mL) was added,[118] followed by a solution of dimesylate **37** (0.257 g, 0.458 mmol) in THF (3 mL). After 1 h the mixture was again refluxed for 30 min. It was then cooled to room temperature and partitioned between hexane (100 mL) and water (100 mL). The organic phase was washed with water (2 × 50 mL) and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (2 × 20 cm), using 35:65 CH_2Cl_2-hexane, gave **35** (0.043 g, 25%) as a pure (^1H NMR, 200 MHz), colorless oil, spectroscopically identical to a known sample.

(b) $NaB(OMe)_3H$/DMF and diphenyl diselenide.

DMF (5 mL) was added to a mixture of solid $(PhSe)_2$ (0.075 g, 0.240 mmol) and $NaB(OMe)_3H$ (0.072 g, 0.056 mmol). The mixture was refluxed for 45 min and then cooled to room temperature. Dimesylate **37** (0.112 g, 0.200 mmol) in DMF (3 mL) was added, and the mixture was warmed to 60 °C for 2 h and then stirred at room temperature for 36 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 × 20 cm), using 35:65 CH_2Cl_2-hexane, gave **35** (0.022 g, 29%) as a pure (^1H NMR, 200 MHz), colorless oil, spectroscopically identical to a known sample.

2',3'-Didehydro-2',3'-dideoxy-5'-*O*-(triphenylmethyl)-uridine (41).[15]

40 **41**

(a) $NaBH_4$/EtOH and di(2,4-dimethoxyphenyl)ditelluride (75).

Absolute EtOH (5 mL) was added to a mixture of solid **75** (0.067 g, 0.127 mmol) and $NaBH_4$ (0.011 g, 0.714 mmol). The mixture was stirred at room temperature for 20 h, by which time it was colorless. Dimesylate **40** (0.069 g, 0.106 mmol) in EtOH (2 mL) was added and stirring at room temperature was continued for 20 h. The mixture was evaporated and flash chromatography of the residue over silica gel (1 × 20 cm), using 3:97 MeOH-CH_2Cl_2, gave **41** (0.018 g, 38%) as a pure (^1H NMR, 200 MHz), colorless oil, spectroscopically identical to a known[15] sample.

(b) Et_3BHLi/THF and di(2,4-dimethoxyphenyl)ditelluride (75).

Et_3BHLi (1 M in THF, 0.28 mL, 0.28 mmol) was added to solid **75** (0.074 g, 0.140 mmol) and the mixture was stirred at

room temperature for 6 h. Dimesylate **40** (0.075 g, 0.117 mmol) in THF (1 mL) was added dropwise, and the mixture was stirred at room temperature for 20 h and then evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 5:3.5:1.5 CH_2Cl_2-PhMe-MeCN, gave **41** (0.035 g, 66%) as a pure (^{1}H NMR, 200 MHz), colorless oil, spectroscopically identical to a known[15] sample.

(c) Na/naphthalene/THF and di(2,4-dimethoxyphenyl)-ditelluride (75).

A Na/naphthalene solution in THF (1 M with respect to Na and naphthalene, 0.4 mL, 0.4 mmol sodium naphthalenide) was added to ditelluride **75** (0.091 g, 0.171 mmol) in THF (1 mL). The mixture turned clear by the end of the addition. Dimesylate **40** (0.100 g, 0.156 mmol) in THF (1 mL) was added and the mixture was stirred at room temperature for 1 h and then evaporated. Flash chromatography of the residue over silica gel (1 × 20 cm), using 5.5:2.5:2 CH_2Cl_2-PhMe-MeCN, gave olefin **41** (0.027 g, 38%) as a pure (^{1}H NMR, 200 MHz), colorless oil, spectroscopically identical to a known[15] sample.

(c) $NaB(OMe)_3H$/DMF and di(2,4-dimethoxyphenyl)-ditelluride (75).

DMF (5 mL) was added to a mixture of solid ditelluride **75** (0.148 g, 0.280 mmol) and $NaB(OMe)_3H$ (0.084 g, 0.654 mmol). The mixture was warmed to 80 °C until the solution

was clear (45 min). Dimesylate **40** (0.150 g, 0.233 mmol) in DMF (3 mL) was added and the mixture was stirred at room temperature for 12 h and then evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 5.5:2.5:2 CH_2Cl_2-PhMe-MeCN, gave **41** (0.001 g, 0.9%) as a pure (^{1}H NMR, 200 MHz), colorless oil, spectroscopically identical to a known[15] sample.

(d) $Et_3BHLi/NaBH_4$/EtOH and di-2-thienyl ditelluride.

Et_3BHLi (1 M in THF, 0.34 mL, 0.34 mmol) was added to a stirred and cooled (0 °C) solution of di-2-thienyl ditelluride[79] (0.072 g, 0.171 mmol) in THF (2 mL) and the mixture was stirred at 0 °C for 2 h. Dimesylate **40** (0.100 g, 0.156 mmol) in THF (2 mL) was added and stirring was continued at 0 °C for 1 h. None of the desired product was formed [tlc, silica, 5:3:2 MeCN-CH_2Cl_2-PhMe]. A solution of $NaBH_4$ (0.013 g, 0.342 mmol) in absolute EtOH (2 mL) was added, and stirring at 0 °C was continued for 1 h. The mixture was kept at room temperature for 12 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 × 20 cm), using 5:3:2 MeCN-CH_2Cl_2-PhMe, gave **41** (0.030 g, 42%) as a pure (^{1}H NMR, 200 MHz), colorless oil, spectroscopically identical to a known[15] sample.

Electrochemical Apparatus

The electronic equipment used to run the cells and to run cyclic voltammograms was as follows: EG & G Model 175

Universal Programmer, EG & G Model 174A Polarographic Analyzer, Amel Model 551-Potentiostat, and an EG & G Model RE 0074 X-Y Recorder.

Two types of cells were used. The first type[119] was used for entries 1 & 2 (Table 2). It was an H-type cell with two compartments. There were two ion exchange membranes separating the compartments, Ionac MA 3475 (anodic side) and MC 3470 (cathodic side). The counter electrode was a platinum wire with a Pt grid attached (10 x 20 mm). The working electrode for entry 1 was a Te-graphite electrode prepared similarly to a Se electrode,[87] and for the remaining entries a Pt wire was used with a Pt grid (10 x 20 mm) attached. A standard calomel electrode was used in the cathode compartment and all potentials were referenced to this. The electrolyte used is recorded in Table 2.

A second type of cell was used for entries 3-32, and it differs from the first in that a glass frit was used to separate the two compartments. Each side of the cell contained *ca.* 15 mL of solution, and the solution in the cathode compartment was stirred by a small magnetic stirring bar. Dimethyl malonate was used as an additive,[90] as indicated in the Table. In certain experiments the whole cell was placed in a sonicator.[92]

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54. I would like to thank Raylo Chemicals for generously supplying our nucleoside substrates as indicated.

55. Hydrogenation gave the saturated compound **94** (61%), as described in the experimental section.

56. Compound **52** was not obtained absolutely pure. Olefination, hydrogenation to form the saturated compound, and removal of the nitrogen protecting group was performed on the dimesylate **51**, which gave **95** in 43% yield, as described in the experimental section.

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INTRODUCTION - PART 2

The Use of Analogues of Compactin to Lower Blood Cholesterol Levels

The Importance of Cholesterol-Lowering Drugs

The leading cause of death and disability in Western industrialized countries is coronary heart disease,[1] and the major risk factor is an elevated plasma level of low density lipoprotein cholesterol.[2-4] Plasma cholesterol levels can be lowered effectively by controlling endogenous cholesterogenesis because most of the cholesterol in the body is synthesized *de novo*. This approach has been made possible by the discovery of two novel fungal metabolites, mevastatin (compactin) and lovastatin (mevinolin). These compounds are potent inhibitors of HMG-CoA reductase (3-hydroxy-3-methylglutaryl-coenzyme A reductase), which regulates the rate-limiting step in the biosynthetic pathway to cholesterol.[1]

The problems caused by elevated blood levels of cholesterol can be understood in the following way.

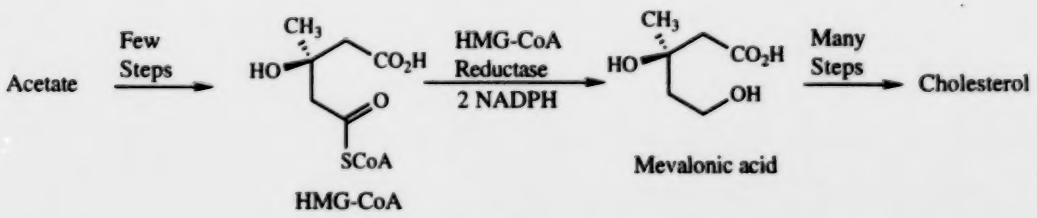
Atheroma, or fatty degeneration of the inner coat of arteries, is due, in part, to lipid deposits – mostly cholesterol esters – on the inner walls of arteries. These deposits lead to constriction of the arteries – a phenomenon known as atherosclerosis – and this ultimately results in coronary heart disease.

Because of the widespread nature of this disease, intense efforts have been made to develop therapeutic agents

to prevent and to treat atherosclerosis. Most approaches have involved attempts to lower plasma cholesterol levels, and there is strong supporting evidence for this rationale.[5,6] It has been clearly demonstrated that reduction of low density lipoprotein cholesterol through dietary modification and treatment with the bile acid sequesterant colestyramin, either alone or in combination, diminishes the incidence of morbidity and mortality in hypercholesterolemic men who were judged to be at high risk for coronary heart disease.[5,6] Nevertheless, these treatments fail to lower elevated plasma low density lipoprotein cholesterol to the desired extent, especially in patients with familial hypercholesterolemia.[1] (Familial hypercholesterolemia is caused when mutations of the gene encoding for the low density lipoprotein receptor result in impaired degradation of low density lipoprotein.[7]) In order to lower the levels of low density lipoprotein further, control of endogenous cholesterogenesis could be a potentially more effective procedure.

How Blood Cholesterol Levels Can Be Controlled

Cholesterol is synthesized from acetate units, as shown in Scheme 1.



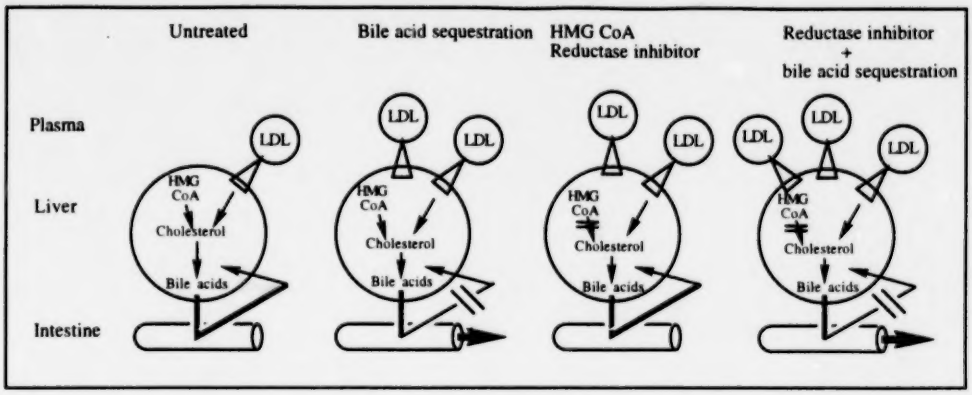
Scheme 1

The rate-limiting step in this pathway is regulated by the enzyme HMG-CoA reductase (3-hydroxy-3-methylglutaryl-coenzyme A reductase), which catalyzes the conversion of HMG-CoA to mevalonic acid. This enzyme has been the prime target of pharmacological intervention for the control of endogenous cholesterogenesis.

Two major inhibitors of this enzyme are mevinolin and compactin, although the isolation of related inhibitors has also been reported.[8]

The inhibition of HMG-CoA reductase by mevinolin and compactin is reversible and competitive,[1] and neither compound affects the other enzymes involved in cholesterol biosynthesis. In mammalian cells cultured in a medium containing low density lipoprotein cholesterol, the synthesis of other biologically important substances, such as ubiquinone, dolichol and tRNA, which are also derived from mevalonate and are required for cell growth, is not affected even when the activity of the HMG-CoA reductase is severely suppressed (up to 98%) by compactin.[7,9] This observation suggests that these inhibitors are very specific for HMG-CoA reductase and, when used in animals[8] and humans,[10-13] are highly effective hypocholesterolemic agents.

Based on findings by Brown and Goldstein,[7] the therapeutic treatment (including HMG reductase inhibition) of hypercholesterolemia is shown diagrammatically in Scheme 2.



Scheme 2

The therapeutic aim is to lower low density lipoprotein cholesterol levels by increasing the production of low density lipid receptors in the liver. A liver cell normally obtains its cholesterol in a number of ways: uptake of circulating low density lipoprotein via receptor-mediated endocytosis, *de novo* biosynthesis, and from chylomicron remnants. It then converts most of its cholesterol into bile acids. A large portion of the bile acids secreted from the liver is returned to the liver through a process called enterohepatic cycling, and so conversion of cholesterol to bile acids is slowed, as the required supply is met in part by the cycling process. It is well established that the liver is the major site of receptors for low density lipoprotein cholesterol, and production of these receptors is controlled by the demand of the liver cells for cholesterol.[1]

Production of low density lipoprotein receptors in the liver can be increased by inhibition of intestinal reabsorption of bile acids and/or by inhibition of endogenous

cholesterol synthesis. When drugs are used to control endogenous cholesterol synthesis the absolute amount of low density lipoprotein cholesterol entering the liver through a receptor pathway is not altered during the drop in concentration of low density lipoprotein cholesterol in plasma. The fall in plasma low density lipoprotein cholesterol levels would normally lower the rate of low density lipoprotein cholesterol entering the liver, but this potential result is offset by the increase in low density lipoprotein receptors. The important net effect, however, is that the plasma low density lipoprotein cholesterol levels are lowered.

Effectiveness of HMG-CoA Reductase Inhibitors

In practice, the ingestion of bile acid resins (*e.g.*, colestyramine and colestipol) causes plasma low density lipoprotein cholesterol levels to decrease by stopping reabsorption of bile acids and thereby increasing the metabolism of cholesterol. The decrease in plasma low density lipoprotein cholesterol levels is about 20%,[5,6] which is not large enough to be therapeutically useful. Using HMG-CoA reductase inhibitors such as mevinolin[11-13] and compactin[10] can be more effective. Compactin lowers plasma low density lipoprotein cholesterol levels by 33% and, when used in conjunction with colestipol, a drop of 46% is observed.[12]

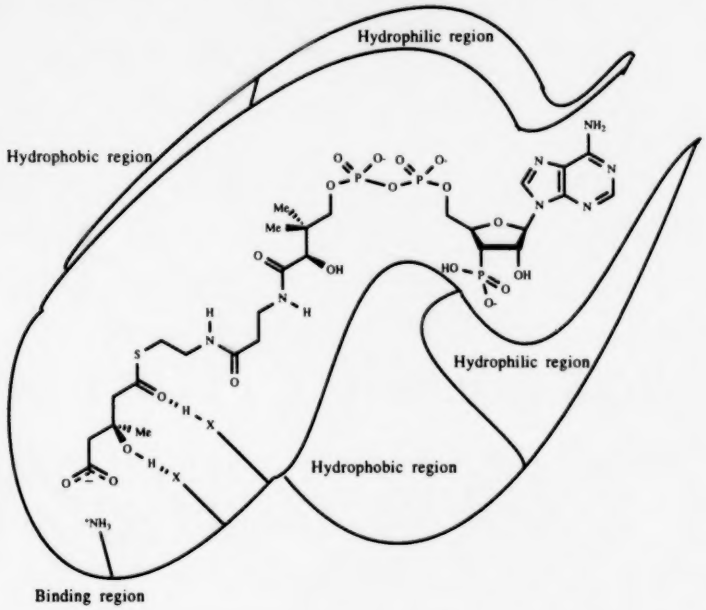
Binding Site Hypothesis

The process by which stimulation of low density lipoprotein receptor activity ultimately lowers plasma low density lipoprotein cholesterol levels without grossly altering the cholesterol supply to cells is an important phenomenon, and its recognition has lead to significant efforts towards the synthesis of mevinolin, compactin, and related analogues.[14]

In designing synthetic analogues to inhibit HMG-CoA reductase some guidance can be obtained from what is known about the binding of the natural substrate to the enzyme. The structural similarity between compactin and HMG-CoA or mevalonic acid is clear from examining the open form of the lactone side chain in both compactin and mevinolin. However, since binding of HMG-CoA, the natural substrate, to the enzyme is ~10^4 weaker than the binding of mevinolin or compactin, the perhydronaphthalene moieties must account for the additional binding energy of the fungal metabolites.[15]

A hypothetical HMG-CoA reductase binding site[16] is shown in Scheme 3. The HMG-CoA is bound principally by the

Hypothetical HMG CoA Reductase Binding site



Scheme 3

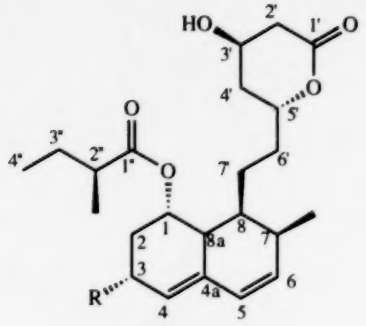
coulombic and hydrogen bond attractive forces in the "binding region", and by the same attractive forces in the "hydrophilic region." The forces binding the two ends of the natural substrate to the enzyme are sufficient to outweigh the repulsive interactions in the hydrophobic regions within the pocket. An interesting question one might ask is why HMG reductase has a hydrophobic section, and a possible answer is that this region has evolved so that the reaction product, CoA, is not bound too strongly. The CoA would only be bound in the hydrophilic region and would be repelled in the hydrophobic region. This arrangement would assist in ushering the CoA from the binding site, thus facilitating turnover.[16] The presence of the hydrophobic region also

serves to explain why mevinolin and compactin bind more strongly to HMG-CoA reductase than does HMG-CoA. The strong attraction of the hydrophobic region of the enzyme to the hydrophobic part of mevinolin and compactin suggested that synthetic analogues with this hydrophobic moiety should be prepared; many such compounds have been made, and their structure activity relationships were considered in the selection of our own analogue.

Structure-Activity Relationships of Analogues of HMG-CoA Reductase Inhibitors

Many analogues of mevinolin and compactin have been synthesized with the hope of finding a more potent inhibitor that is also safe for human consumption. Extensive structure activity studies have been reported by many pharmaceutical companies, especially Merck Sharp & Dohme,[17,18] Sandoz Research Institute,[19] Hoechst,[20] Bristol-Myers Squibb,[21,22] Warner-Lambert Company,[23,24,25,26,27] Rhone-Poulenc Rorer,[28] SmithKline Beecham,[29,30] and Bayer.[31]

The structures of mevinolin and compactin, and their analogues can be divided into four moieties: (1) the lactone or the dihydroxy acid, (2) the bridging portion that joins the lactone to the lipophilic part, (3) the perhydronaphthalene ring, and (4) the side chain ester.[32]



1 R = CH_3
2 R = H
3 R = OH

Scheme 4

Biological activity is lowered by the following changes to the mevinolin or compactin structure:

(1) Inversion of stereochemistry of either the 3'- or 5'-hydroxyl groups.[33]

(2) Oxidation of the 5'-oxygen to the ketone.[33]

(3) Oxidation of the 5'-oxygen *and* replacement of C(6') by an oxygen (biologically inactive).[33]

(4) Introduction of CH_2 between C(1') and C(2').[1]

In contrast, replacement of the C(3') hydrogen by a methyl group (with preservation of stereochemistry) does not alter the activity, at least as judged by studies with analogues in which the perhydronaphthalene unit had been replaced.[17]

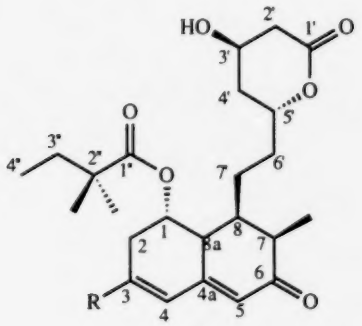
One can conclude from the above data that the lactone is essential for biological activity.[34]

Studies of analogues showed that activity is lowered if there is a double bond in the bridging portion [at C(6')-C(7')], or if the stereochemistry at C(1), C(7), C(8), and C(8a) is simultaneously reversed in the perhydronaphthalene portion.[33] However, when the double bond between C-4 and C-4a of mevinolin is hydrogenated, the product is more active,[33] although the ring junction stereochemistry must be *trans* to preserve activity.[1]

The presence of an axial methyl [at C(7)] is also important. Two almost identical compounds were compared with and without the methyl, and the former was found to be much more active.[35]

Mevinolin (**1**) (Scheme 4) is 4-5 times more active than compactin[36] (**2**). Another highly active C(3)-functionalized compound is pravastatin (**3**).

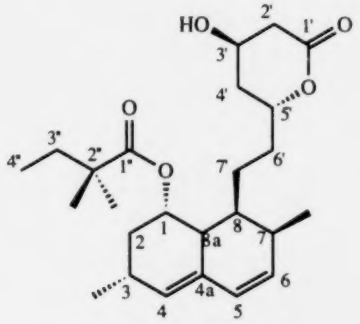
Compound **4** (Scheme 5) has also been found to be active. The most obvious characteristics of this compound are that



4

Scheme 5

the double bond positions are shifted to C(3)-C(4) and C(4a)-C(5) and there is an oxo function at C(6) and an additional methyl at C(2"). The compound is 6-7 times more active than symvastatin (**5**)[37] (Scheme 6).



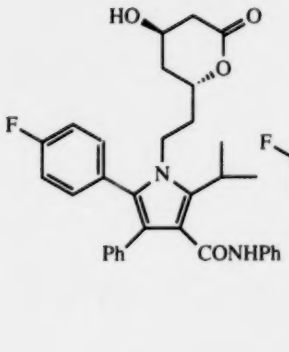
Symvastatin
5

Scheme 6

Finally, changes in the side chain ester unit have also been examined. The stereochemistry at C(2") of the side chain is not important. In fact, the opposite stereochemistry, or the presence of two methyl groups at C(2"), generates more active compounds.[1] Various groups have been attached to the C(1) oxygen function of the perhydronaphthalene, and most of the resulting compounds are quite active.[38]

A very large number of potential inhibitors have been made that resemble only a small portion of mevinolin and compactin – usually just the lactone portion – and some of the more active are discussed below.

HMG-CoA Reductase Inhibitors from SAR Studies



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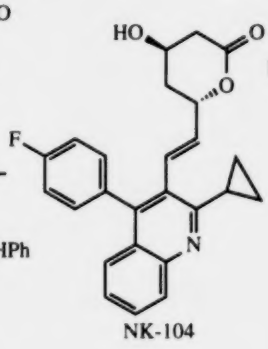
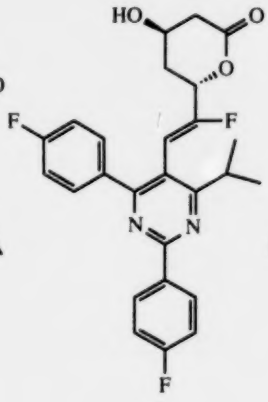


NK-104

7



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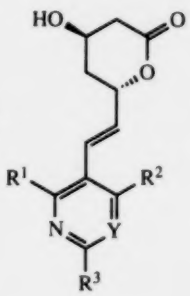

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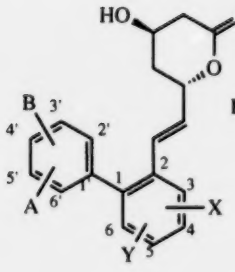

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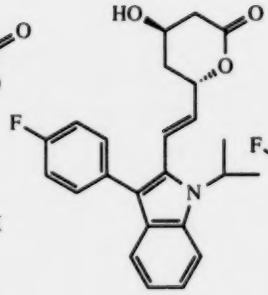

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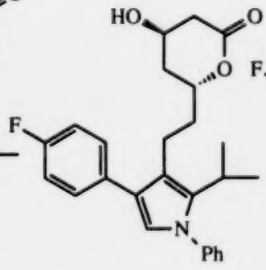

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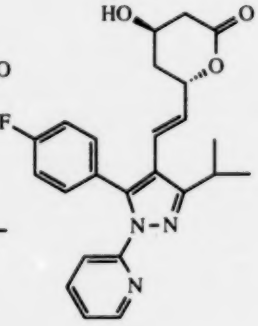

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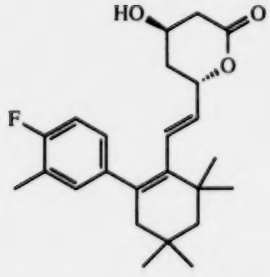

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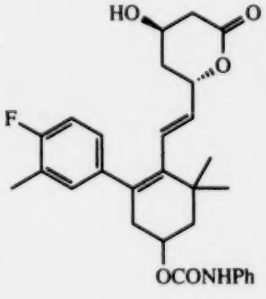

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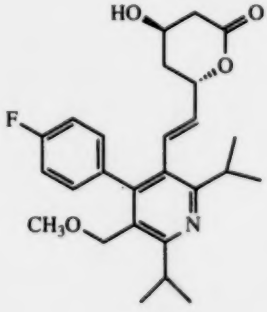


16

Scheme 7

Examples **6** through **16** (Scheme 7) are all inhibitors of HMG-CoA reductase, and they are all at least as active *in vitro* as mevinolin and compactin. Compound **6** is undergoing clinical trials[39] and is especially noteworthy because it differs from most of the other compounds in that the δ-lactone moiety is attached to a heteroaromatic group via the heteroatom. Compound **7**, known as NK-104, was recently shown to be 10-fold more potent than pravastatin.[40] Example **8** was found to be more potent than mevinolin in the inhibition of solubilized microsomal rat liver HMG-CoA reductase.[41] Example **9** has been modified slightly, to afford a range of derivatives (in which R^1, R^2, R^3 and Y are varied). The compounds are 1 to 10 times as potent as mevinolin.[42] The range of substituents studied was: R^1 = isopropyl; R_2 = *para*-fluorophenyl, and R^3 = methyl, *i*-propyl, *t*-butyl, *c*-C_6H_{11}, C_6H_5, *para*-fluorophenyl, or 2,5-dimethylphenyl, and Y = CH or N.

Compound **10** was studied extensively[43] with various combinations of the substituents A, B, X, and Y.

All these analogue studies on **10** revealed only a few compounds more potent than compactin. These highly active compounds had: A = 3'-Me, 4'-F, 3'- and 5'-Me or 3'-Cl; B = H, 5'-Me, 4'-F, 4'-Cl, or 5'-Cl; X = 3-Cl or 3-Me; and Y = 5'-Cl, 5-Me, or 6-Me.[43]

Analogue **11**, fluvastatin, is 10 times more potent than mevinolin *in vitro* but of only equal potency in lowering cholesterol in patients.[37]

Example **12** is 3-5 times more potent than mevinolin both *in vitro* and *in vivo*.[37]

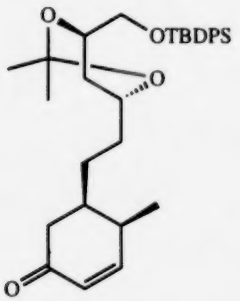
Analogue **13** is 5-10 times more potent than compactin *in vitro* while **14**, dalvastatin, is approximately equal to mevinolin *in vivo* and is undergoing clinical trials.[37]

Compound **15** is 5 times more potent *in vitro* than mevinolin,[37] while **16** is 110 times more potent than mevinolin *in vitro* and is undergoing clinical development.[37]

Semisynthetic Target Analogue

As is clear from the above examples the huge effort devoted to the development of new and potent analogues of mevinolin to inhibit HMG-CoA reductase has led to a number of promising candidates.

Against the background of the above information, and also taking into account the fact that we had previously

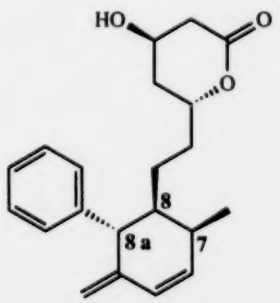


17

Scheme 8

degraded natural compactin and mevinolin into the enone **17**, we tried to select a potential analogue that might be made

conveniently from **17**, so as to afford a *semisynthetic* compound. It was clear from the structure-activity studies that the lactone unit should be preserved,[34] and that it would be of possible benefit to attach at C(8a) (mevinolin numbering) an aromatic ring (*cf.* **6** - **16**). The stereochemistry at C(8a) was set to be the same as in the natural inhibitors – the opposite stereochemistry would make a very large change to the conformation of the system. We were left, then, with the decision of how to modify the carbonyl group of **17**, and we decided to convert it into a simple carbon double bond appendage so as to imitate the diene portion of mevinolin and compactin. These considerations led us to define **18** as the semisynthetic target. Incidentally, this compound does, of course, preserve the C(7) methyl



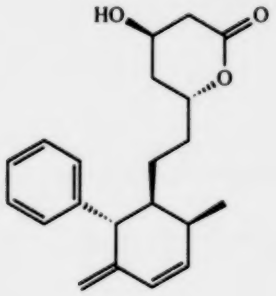
18

Scheme 9

substituent, which has been found to be a beneficial[35] feature.

DISCUSSION PART 2

As indicated above, we set out to prepare the semisynthetic analogue **18**.



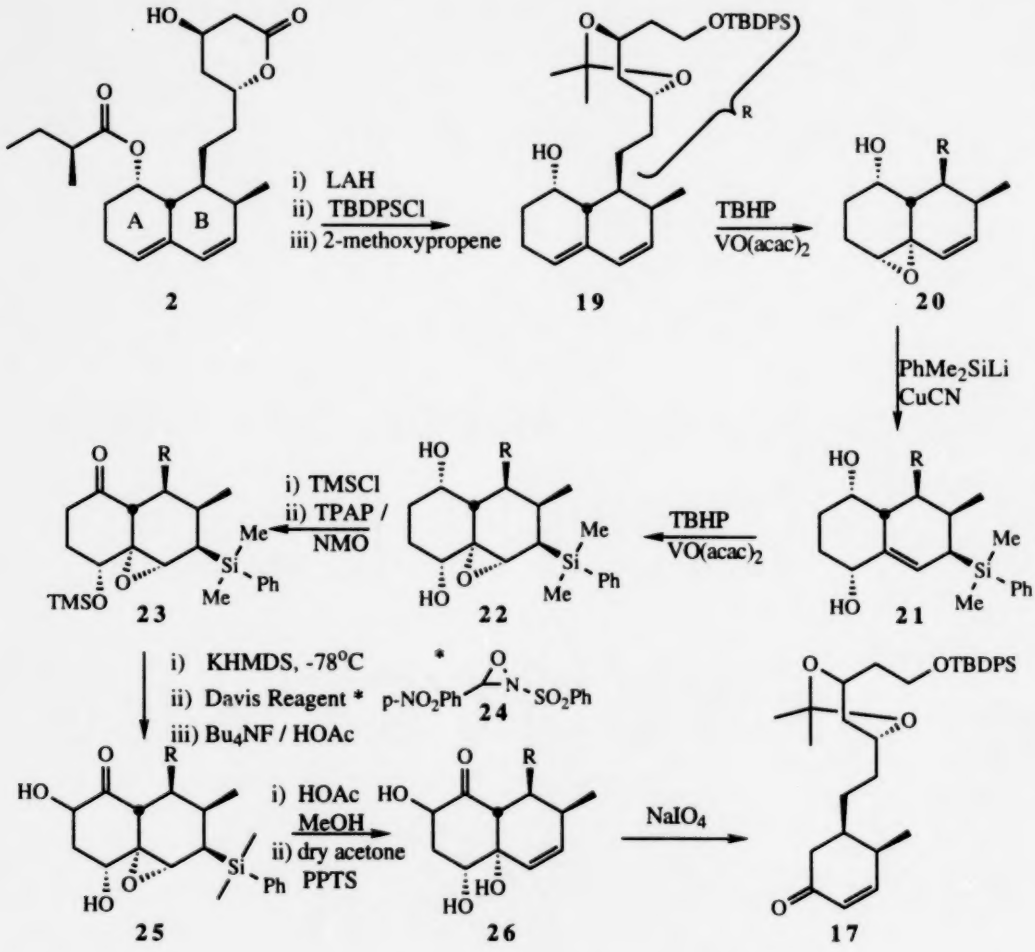
18

Scheme 9

The work involves two phases: degradation of natural compactin to enone **17**,[44] and then elaboration of this substance to the target **18**.

Degradation of Compactin

Chengzhi Zhang of this laboratory had worked out a procedure,[45] which I will discuss briefly, for degrading compactin into **17**. This compound was an intermediate used in the total synthesis of mevinolin, compactin, and 3-ethyl compactin.[46,47] The general route he followed is shown in Scheme 10. I will discuss in detail only the problems I encountered in repeating the degradation, and, of course, the solutions to these problems.

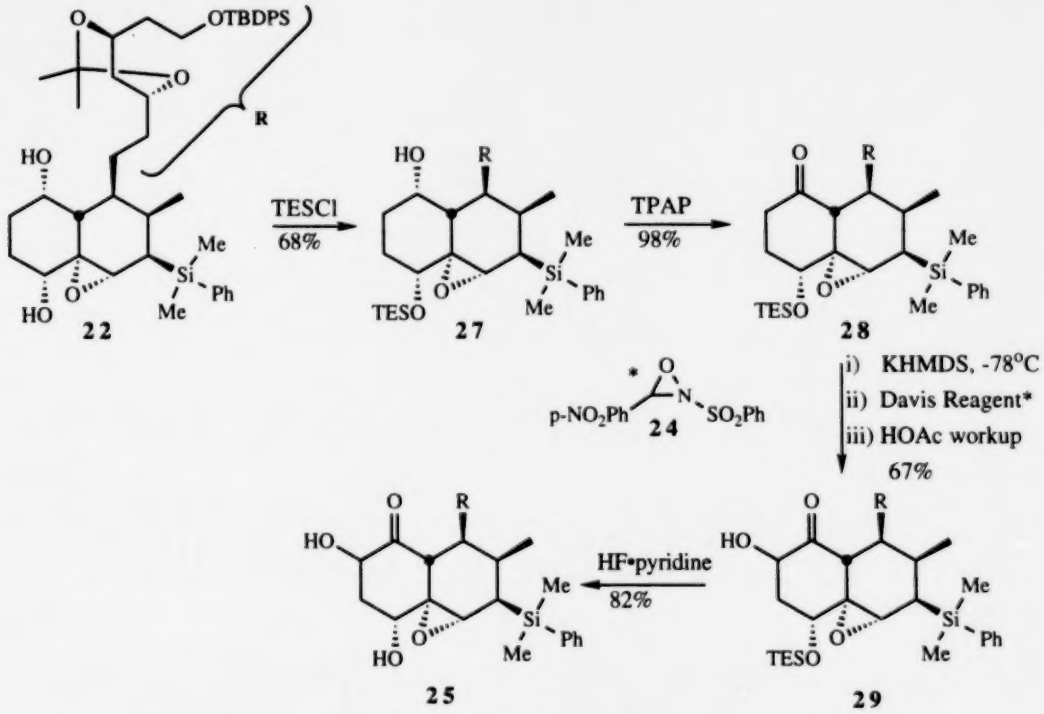


Scheme 10

Compactin (**2**) was reduced with lithium aluminum hydride, and the resulting tetrahydroxy compound was selectively silylated and ketalized (using 2-methoxypropene in the presence of pyridinium *p*-toluenesulfonate). This form of protection of the lactone side arm allowed ring A to be degraded, as shown (Scheme 10). Homoallylic epoxidation and introduction of the dimethylphenylsilyl unit, using $PhMe_2SiLi$ and CuCN, afforded **21**. Next, allylic epoxidation and

selective silylation of the C(4) equatorial hydroxyl allowed the free hydroxyl at C(1) to be oxidized, using *N*-methylmorpholine-*N*-oxide and a catalytic amount of tetrapropylammonium perruthenate. Oxidation α to the carbonyl group of **23** was performed by treating the potassium enolate of **23** with Davis' reagent[48] (**24**) to afford, after deprotection with tetrabutylammonium fluoride, compound **25**. Acetic acid and methanol were then used to form the trihydroxy ketone **26**. During this process there is some slight loss of the ketal group, but this is easily replaced by treatment of the crude reaction product with dry acetone and *p*-toluenesulfonic acid. The trihydroxy ketone **26** was converted to the required enone **17** by exposure of an aqueous methanol solution of **26** to the action of sodium periodate.

The selective silylation of **22** to **23**, using trimethylsilyl chloride, proved to be difficult because the product is very sensitive to hydrolytic loss of the trimethylsilyl group. We decided to try a triethylsilyl protecting group instead, as shown in Scheme 11.



Scheme 11

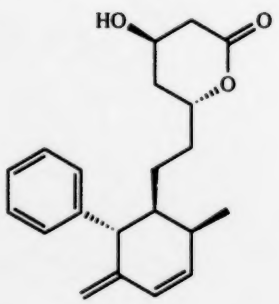
The triethylsilyl-protected compound was much more stable and no difficulties were experienced in performing the oxidation to **28**, and the subsequent α-oxidation to **29**. However, this smooth sequence was achieved at the cost of incurring difficulties in removing the triethylsilyl group. It was stable to the action of tetrabutylammonium fluoride, or methanolic acetic acid, or to mixtures of the two – at least under the mild conditions tried. Eventually HF-pyridine[49] was found to work well (82% yield) for selective deprotection. This route took one extra step because the triethylsilyl group was not removed by treatment with acetic acid. Because of this extra length, I re-explored the use of

the trimethylsilyl protecting group and found that it was not hydrolyzed when *filtration* (through silica) of the crude reaction mixture (obtained from attachment of the trimethylsilyl group) was performed instead of regular flash chromatography. Chengzhi Zhang's route was then accepted as the method of choice with this slight adjustment in procedure.

With the required enone in hand we were now in a position to attempt the preparation of a semisynthetic analogue.

Synthesis of the Semisynthetic Analogue 18

The key step in the preparation of the semisynthetic analogue **18** is the introduction of the phenyl group with the correct stereochemistry, and three approaches were explored to deal with this step.



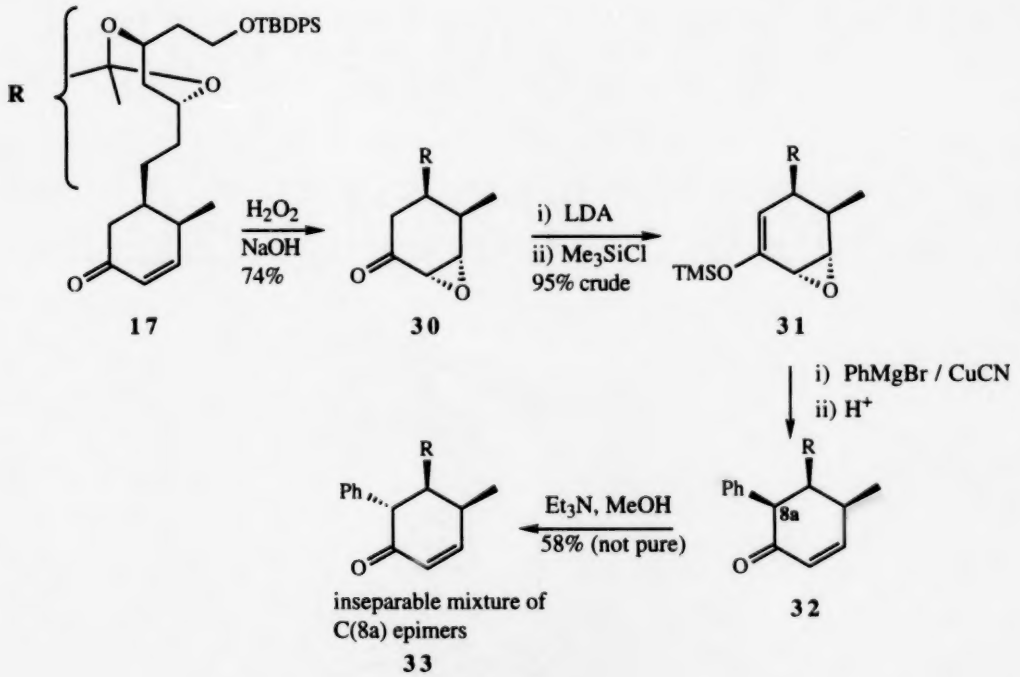
18

Scheme 9

First Approach

The first promising approach was examined by Gil. V. J. da Silva,[50] after he had made a number of attempts at direct ketone arylation.[50]

His procedure for introduction of the phenyl group is summarized in Scheme 12. Epoxidation was performed first (**17** → **30**) and the derived silyl enol ether was then formed (**30** → **31**), allowing introduction of the phenyl group by treatment



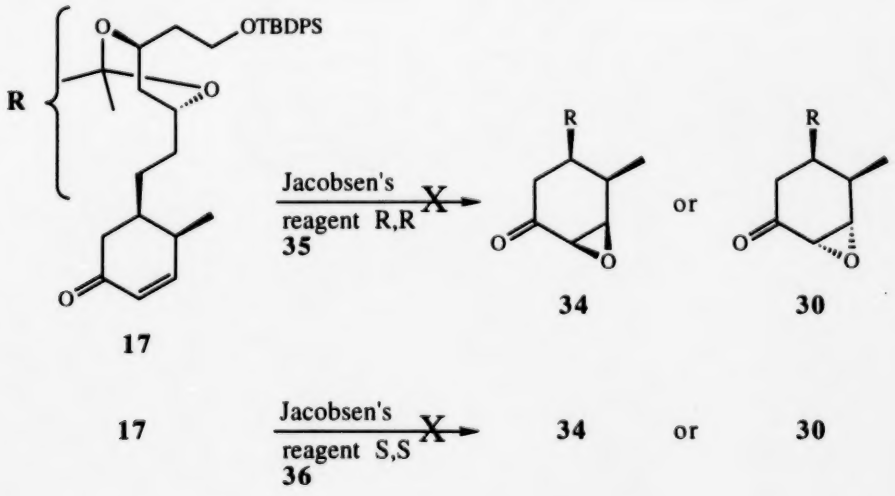
Scheme 12

with phenylmagnesium bromide in the presence of cuprous cyanide. This procedure was based on prior literature,[51] and gave a product in which the phenyl group had the undesired stereochemistry. Attempts to epimerize C(8a) (mevinolin

numbering) were performed using potassium bis(trimethylsilyl)amide/ammonium chloride, acetone/*p*-toluenesulfonic acid, silica/methanol, and potasium carbonate/methanol. Some epimerization did take place but the mixture was inseparable in the chromatographic systems we examined. Since the stereochemistry of the phenyl group is determined by the stereochemistry of the parent epoxide,[51] we decided to prepare the epimeric epoxide so as to obtain directly the desired phenyl ketone, and our next approach is based on the selective epoxidation of enone **17** from the β-face.

Second Approach

Jacobsen's reagents [chiral manganese(III) complexes] are known to perform selective epoxidations on conjugated *cis* disubstituted olefins.[52,53] This selective epoxidation was attempted, as shown in Scheme 13. Enone **17** was treated



17 **34** **30**

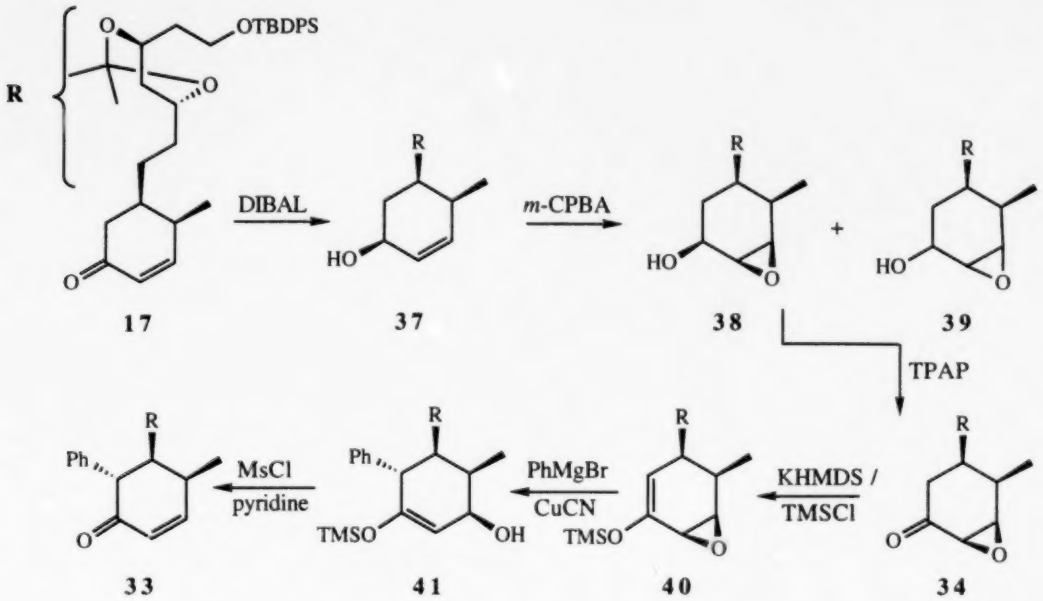
17 —Jacobsen's reagent S,S **36**→ **34** or **30**

Scheme 13

with sodium hypochlorite and *R,R*-(-)-*N,N'*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III) chloride[54] (**35**), using a literature procedure,[53] but only the starting enone was recovered. The *S,S*-(+)-analogue **36** was tried using the same procedure and it gave starting material also. In view of these observations, we decided to prepare the required β-epoxide using a hydroxyl-directed oxidation, as described in the next section.

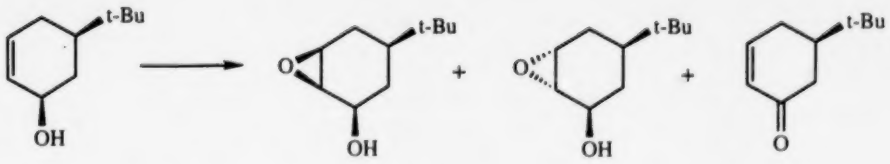
Third Approach

Our third approach starts with stereoselective reduction of the C(3) carbonyl to afford a β-alcohol which, in turn, allows a stereocontrolled allylic epoxidation to be carried out. The stereochemistry of the β-epoxide sets up the molecule for introduction of the phenyl group from the under face, as shown in Scheme 14.



Scheme 14

Diisobutylaluminum hydride reduction (Scheme 14) served to deliver the hydride from the less hindered face to give the desired allylic alcohol **37**. Sharpless epoxidation, using vanadyl acetylacetonate, however, gave none of the desired product, but careful examination of a review by Sharpless and Verhoeven[55] suggested that *m*-chloroperbenzoic acid should be tried. Teranishi and coworkers described an example[56] (Scheme 15), quite similar to ours, and involving both procedures (V^{+5}/*t*-butylhydroperoxide and *m*-chloroperbenzoic acid).



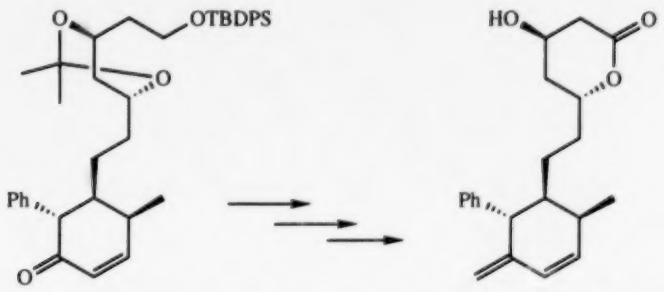
42	43	44	45
V^+, TBHP	18%	1%	74%
m-CPBA	90%	2%	0.5%

Scheme 15

In the case shown in Scheme 15, *m*-chloroperbenzoic acid is a much better reagent. When we tried it on our compound, we obtained the desired product **38** and another isomer **39** in a 2.7:1 ratio, respectively. The isomers were easily separable by flash chromatography and the desired compound (**38**) was oxidized using a catalytic amount of tetrapropylammonium perruthenate and stoichiometric *N*-methylmorpholine-*N*-oxide in dichloromethane. Compound **39** could be converted back to the allylic alcohol using $(EtO)_2PTeNa$ (see experimental). The αβ-epoxyketone formed (**34**) was compared to αβ-epoxyketone (**30**) obtained previously in the first approach. The NMR spectra of the two epoxides differed in signals representing the protons geminal to the epoxide oxygen.

From epoxide **34**, introduction of the phenyl group was accomplished by treatment of the crude trimethylsilyl enol ether **40** with freshly prepared phenylmagnesium bromide, in the presence of copper cyanide, to afford first compound **41**. Treatment of **41** with methanesulfonyl chloride and pyridine then provided the desired phenylated enone **33**.

Having reached this point, the remaining transformations needed to convert the phenylated enone **33** into the



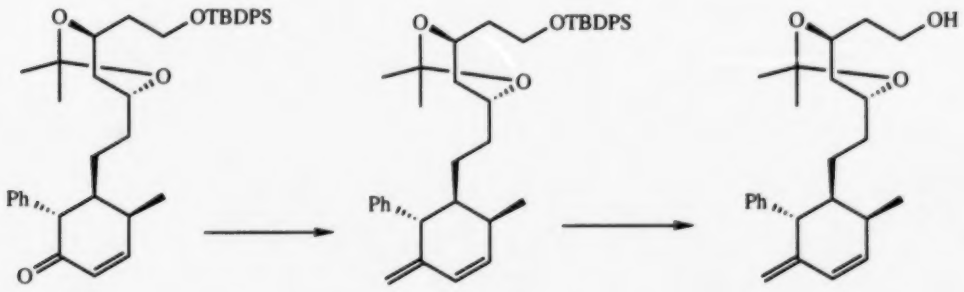
33 **18**

Scheme 16

desired analogue **18** are as follows: the enone carbonyl must be changed into a methylene unit, the protecting groups on the side chain have to be removed, and the side chain elaborated into a lactone.

Completion of the semisynthetic analogue

We dealt first with the replacement of the carbonyl oxygen by a methylene group. It is known that conjugated

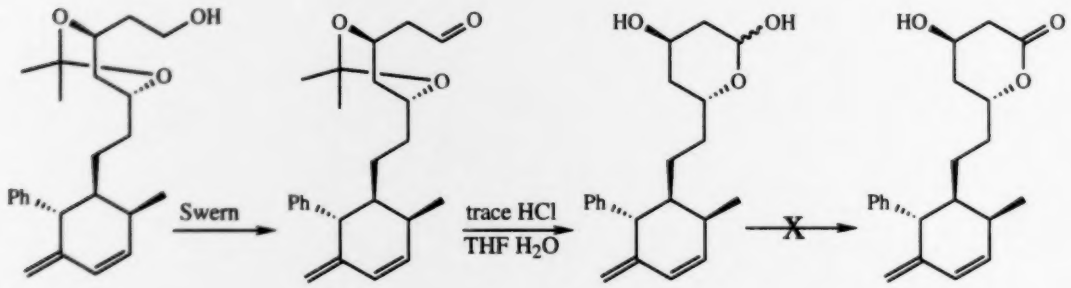


33 **46** **47**

Scheme 17

carbonyls are often more reactive with Tebbe's reagent than with Wittig reagents,[57] and so we tried the Tebbe reagent first and found that it worked well. Deprotection of the primary hydroxyl in the product **46**, using tetrabutylammonium fluoride, gave **47** in nearly quantitative yield.

The remaining oxidation, deprotection and lactonization posed some problems, to our surprise. We attempted several different routes of which that shown in Scheme 18 was the first. We tried to oxidize the primary alcohol **47**, first using tetrapropylammonium perruthenate and *N*-methylmorpholine-*N*-oxide,[58] and also by means of Collins' reagent. The former method did not give any of the desired

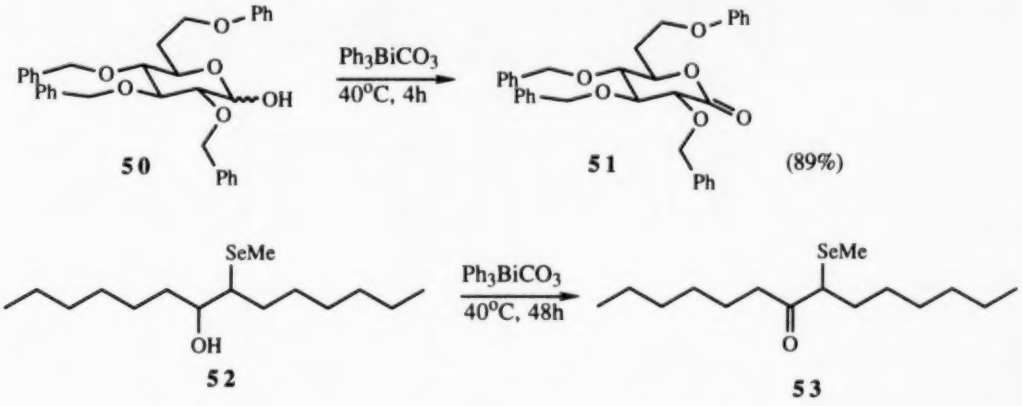


47 **48** **49** **18**

Scheme 18

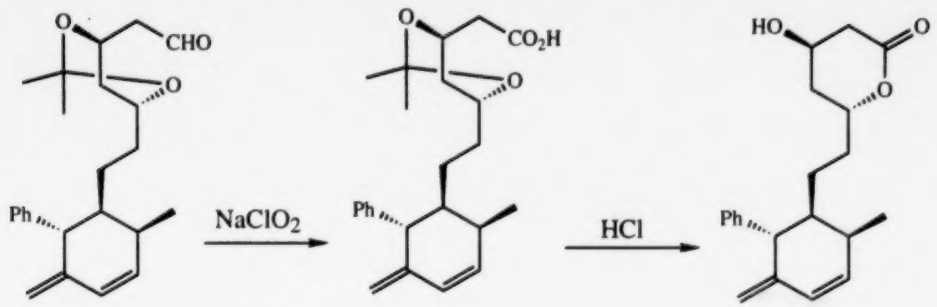
product, and the latter gave a low yield. However, Swern oxidation was quite efficient (96%). Deprotection and cyclization to lactol **49** with a trace of HCl and water in THF, proceeded without incident, and we then attempted to oxidize lactol **49** to lactone **18**, using silver

carbonate/Celite[59] or triphenylbismuth carbonate.[60] Fetizon's reagent (silver carbonate/Celite) was examined because it had been used for this purpose in the total synthesis of mevinolin and compactin.[46] Triphenylbismuth carbonate was used due to its apparent selectivity for oxidizing lactols faster than secondary alcohols[60] (Scheme 19). We drew this conclusion from the fact that lactol **50** required only 4 h for complete oxidation, while the secondary alcohol **52** needed a reaction period of 48 h.



Scheme 19

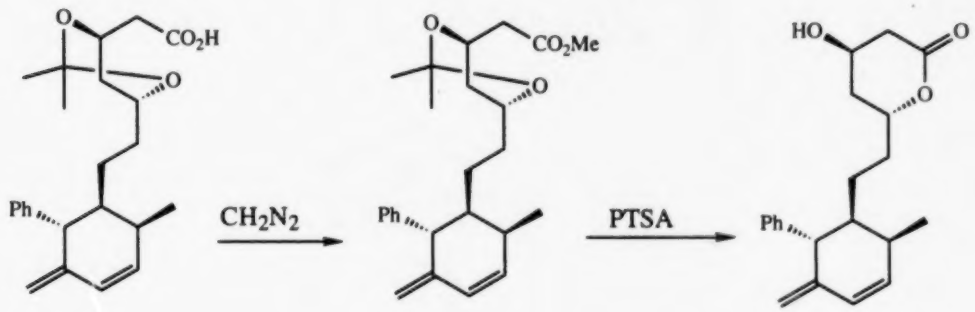
In my case, both reagents failed to give the desired lactone efficiently on a small scale (<3 mg), and we decided to explore another route (Scheme 20). Direct oxidation of alcohol **47** to acid **54**, using pyridinium dichromate[61] did not work efficiently and because of this, we decided to oxidize aldehyde **48** to acid **54**, using sodium chlorite[62] (Scheme 20). This sequence was efficient; but, when we tried to deprotect and cyclize acid **54** to lactone **18** with a trace of HCl in



48 **54** **18**

Scheme 20

aqueous THF, we did not obtain a good yield (12%). Our final strategy was to convert acid **54** to its methyl ester using diazomethane,[63] and then to induce cyclization.



54 **55** **18**

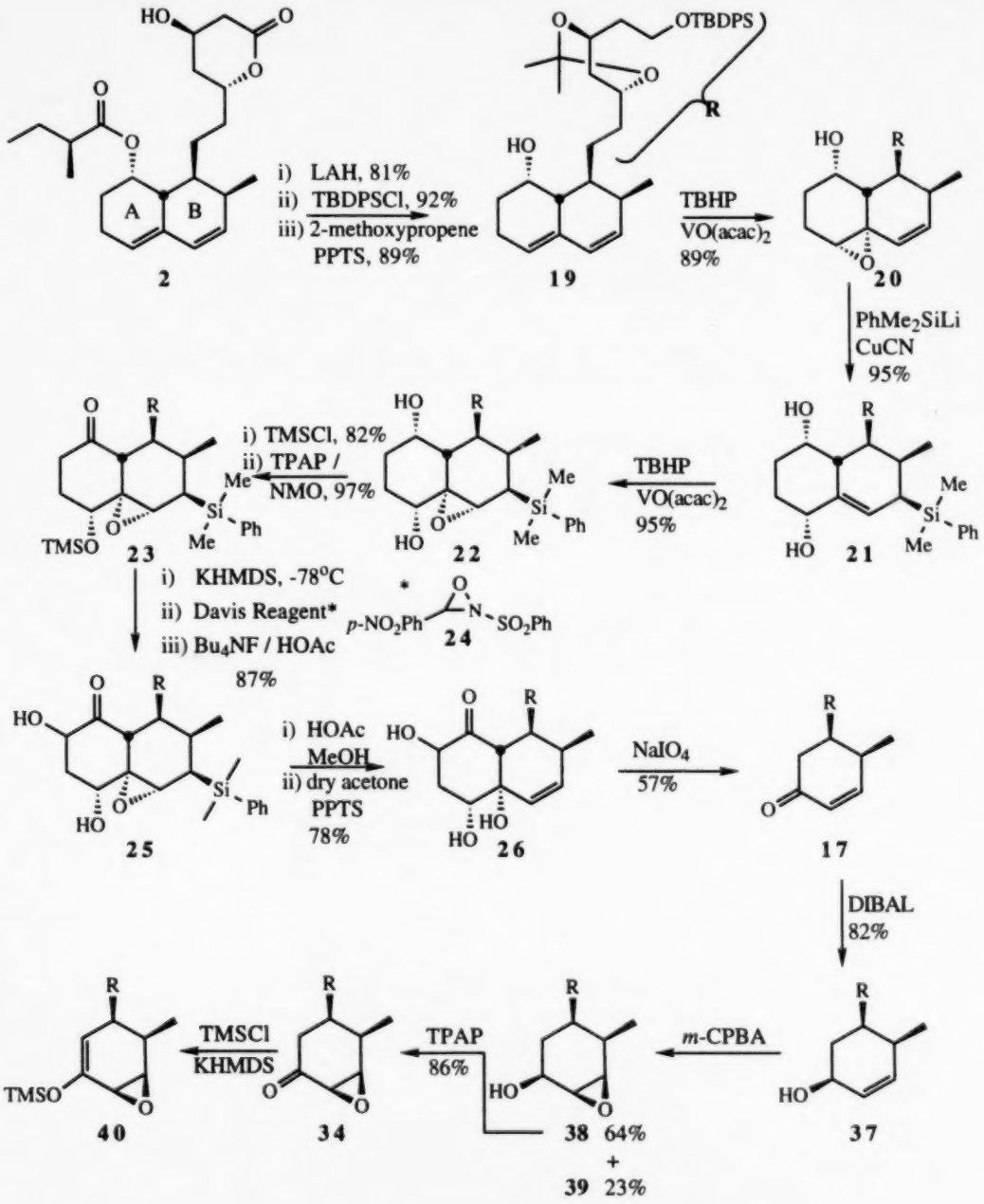
Scheme 21

The esterification worked well (79%), and cyclization using one equivalent of *p*-toluenesulfonic acid in benzene[64] also went in acceptable yield (60%).

Our synthesis of the semisynthetic analogue of mevinolin and compactin was now complete, and a sample of the final product **18** was found to inhibit cholesterol biosynthesis in

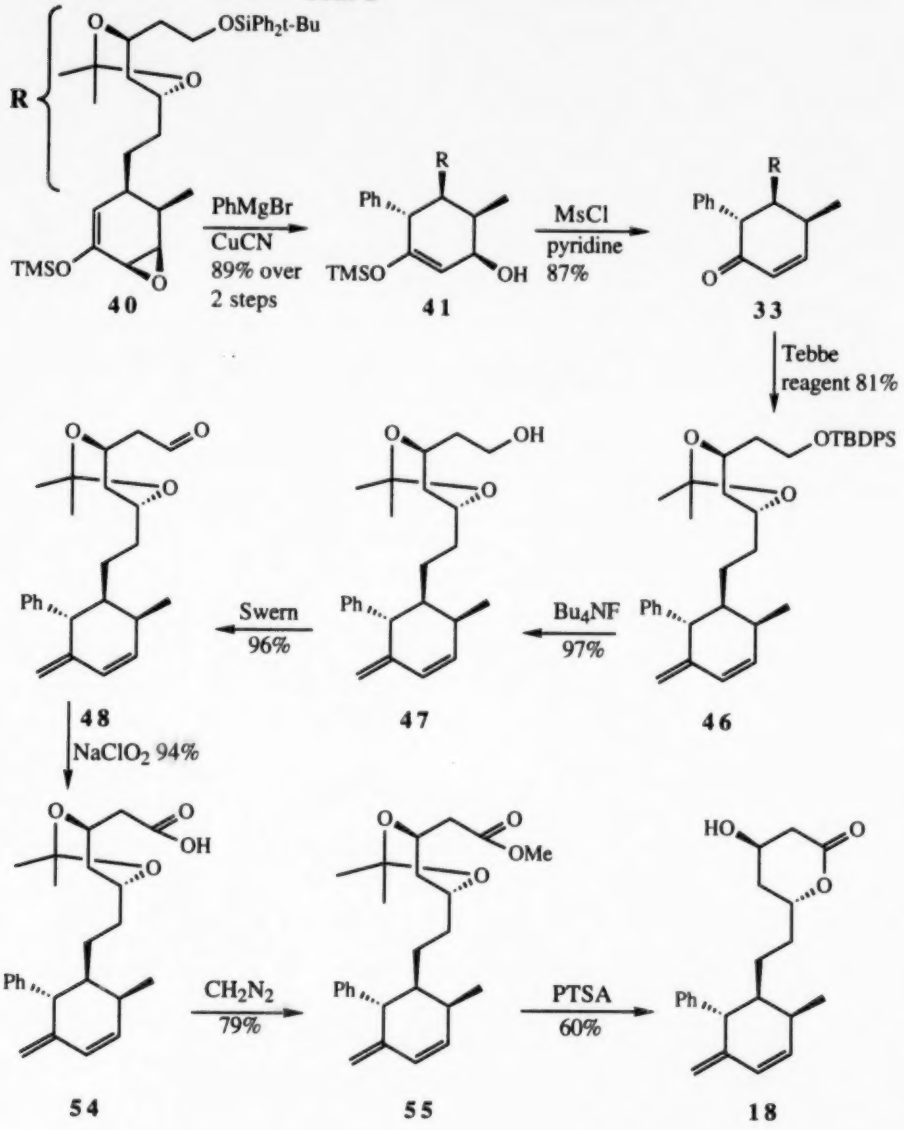
rat liver microsomes. In this test[65] compound **18** has an IC_{50} of 0.54 μg/mL while compactin has an IC_{50} of 10 ng/mL. Schemes 22a and 22b summarize the synthesis of **18**. The route requires 23 steps from compactin, with an overall yield of 1.92%.

Summary of The Synthesis of Semisynthetic Analogue 18



Scheme 22a

Summary of The Synthesis of Semisynthetic Analogue 18
Cont'd



Scheme 22b

Part 2 Experimental Section

General Procedures. Unless stated to the contrary, the following conditions apply: Reactions were carried out under a slight static pressure of Ar that had been purified by passage through a column (3.5 x 42 cm) of R-311 catalyst[66] and then through a similar column of Drierite. All solvents for reactions were dried, as described below. Glassware was dried in an oven for at least 3 h before use (120 °C) and either cooled in a desiccator over Drierite, or assembled quickly, sealed with rubber septa, and allowed to cool under a slight static pressure of Ar. Reaction mixtures were stirred by Teflon-coated magnetic stirring bars.

Hexane used for chromatography was distilled before use.

Products were isolated from solution by evaporation under water aspirator vacuum at, or below, room temperature, using a rotary evaporator.

Microliter syringes were washed with water and acetone, using a suction device to draw the solvents through. Then air was sucked through for 1 min. The solution to be dispensed was drawn up and expelled, and this operation was repeated several times before drawing up the sample to be used. Cannula transfers were always done under slight pressure (Ar), not by suction.

Commercial thin layer chromatography (tlc) plates (silica gel, Merck 60F-254) were used. Spots were detected by

spraying the plate with a solution of phosphomolybdic acid[67] or *p*-anisaldehyde,[68] followed by charring with a heat gun, or by examination under UV light. Silica gel for flash chromatography was Merck type 60 (230-400 mesh).

Dry solvents were prepared under an inert atmosphere and transferred by syringe or cannula. Dry tetrahydrofuran (THF) and Et_2O were distilled from sodium and benzophenone ketyl. Dry PhH was distilled from sodium. Dry Et_3N, CH_2Cl_2, MeOH, MeCN, and pyridine were distilled from CaH_2.

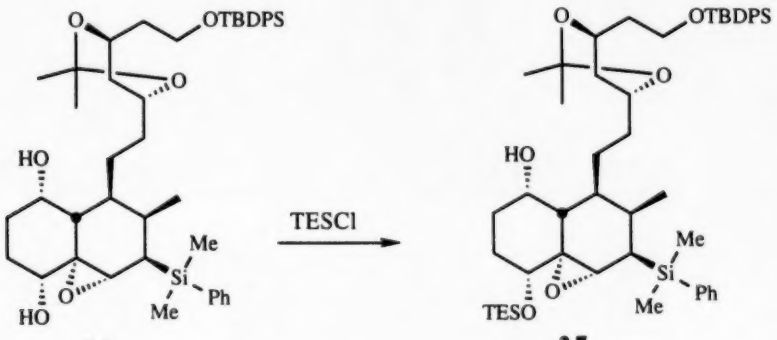
FT-IR measurements were made as casts from the specified solvent using potassium bromide plates.

The symbols s', d', t', and q' used for ^{13}C NMR signals indicate 0, 1, 2, or 3 attached hydrogens, respectively.

Mass spectra were recorded with AEI Models MS-12, MS-50, MS9 (modified), or Kratos MS50 (modified) mass spectrometers.

Microanalyses were performed by the microanalytical laboratory of this Department.

[2R-[2α,3α,4α(4R*,6S*),4aα,5β,8β]]-4-[2-[6-[2-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]ethyl]-2,2-dimethyl-1,3-dioxan-4-yl]ethyl]-2-(dimethylphenylsilyl)octahydro-3-methyl-8-[(triethylsilyl)oxy]-3*H*-naphth[1,8a-b]oxiren-5-ol (27).

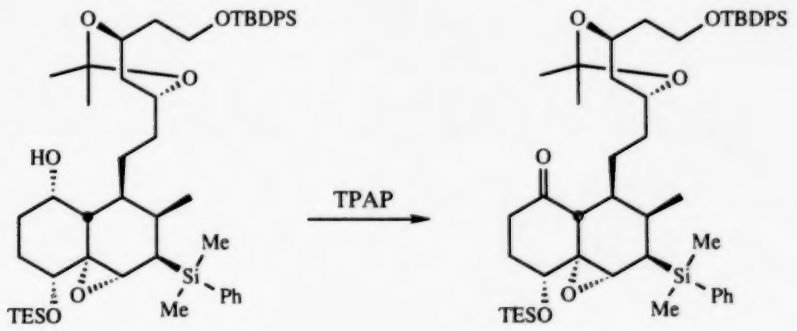


22 27

A 4:1 mixture of Et_3SiCl and Et_3N (40 μL, 0.198 mmol of Et_3SiCl) was added to a stirred and cooled (-78 °C) solution of epoxysilane **22**[69] (0.100 g, 0.132 mmol) and DMAP (*ca.* 6.5 mg, 0.0529 mmol) in CH_2Cl_2 (2.3 mL). Stirring was continued for 5 min and the mixture was then transfered to an ice bath. After 10 min (tlc control, silica, 1:4 EtOAc-hexane), water (1.0 mL) was added and stirring at 0 °C was continued for 10 min. The mixture was diluted with CH_2Cl_2 (20 mL) and the organic layer was washed with water (2 x 10 mL) and brine (1 x 10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 20 cm), using first 1:9 EtOAc-hexane (the mixture containing 1% by volume Et_3N) and then 35:65 EtOAc-hexane (the mixture containing 1% by volume Et_3N), gave **27** (79 mg, 68%) as a pure (^1H NMR, 200 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 3600-3250 cm^{-1}; ^1H NMR

($CDCl_3$, 200 MHz) δ 0.39 (s, 3 H) 0.40 (s, 3 H) 0.50-0.80 (m, 9 H), 0.80-2.15 [m, including singlets at δ 0.80 (3 H), two coincident singlets at δ 1.08 (12 H), singlets at δ 1.38 (3 H), δ 1.42 (3 H), 40 H in all], 2.90-3.02 (br d, J = 9.0 Hz, 1 H), 3.32-3.42 (br s, 1 H), 3.60-3.95 (m, 4 H), 4.02-4.22 (m, 2 H), 7.28-7.50 (m, 9 H) 7.50-7.62 (m, 2 H), 7.62-7.78 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ -2.95 (q'), -2.47 (q'), 5.54 (t'), 7.31 (q'), 12.78 (q'), 19.62 (s'), 20.18 (q'), 25.19 (t'), 27.26 (q'), 28.46 (t'), 28.95 (d'), 30.65 (q'), 32.56 (d'), 32.67 (t'), 35.09 (t'), 37.40 (d'), 37.92 (t'), 39.99 (t'), 41.70 (d'), 52.55 (d'), 60.32 (t'), 65.06 (s'), 66.14 (d'), 67.39 (d'), 69.62 (d'), 70.04 (d'), 98.81 (s'), 128.14 (d'), 128.45 (d'), 129.66 (d'), 130.09 (d'), 134.28 (d'), 134.52 (s'), 136.05 (d'), 138.26 (s'); EIMS m/z calcd for $C_{51}H_{78}O_6Si_3$ 871, found 871. Anal. calcd for $C_{51}H_{78}O_6Si_3$: C, 70.29; H, 9.02. Found: C, 70.19; H, 9.21.

[2R-[2α,3α,4α(4R*,6S*),4aα,8β]]-4-[2-[6-[2-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]ethyl]-2,2-dimethyl-1,3-dioxan-4-yl]ethyl]-2-(dimethylphenylsilyl)hexahydro-3-methyl-8-[(triethylsilyl)oxy]-3*H*-naphth[1,8a-b]oxiren-5(6*H*)-one (28).

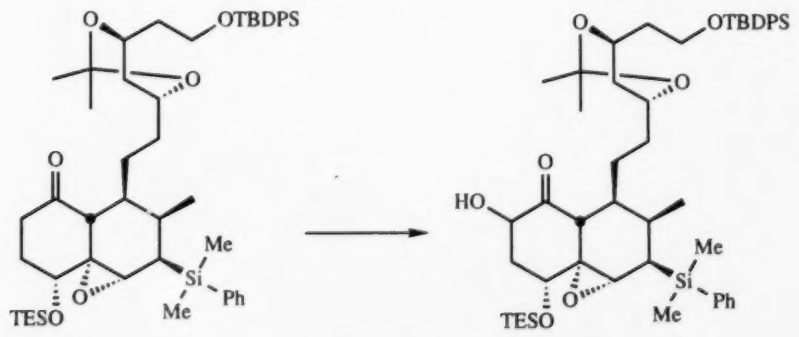


27 **28**

Pr_4NRuO_4 (17 mg, 0.048 mmol) was added in one portion to a stirred and cooled (0 °C) mixture of alcohol **27** (0.417, 0.478 mmol), powdered 4Å molecular sieves (0.251 g), and NMO (0.112 g, 0.957 mmol) in CH_2Cl_2 (20 mL). The cold bath was removed and the mixture was stirred under Ar for 12 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 20 cm), using 5:95 EtOAc-hexane (the mixture containing 1% by volume Et_3N), gave **28** (0.409 g, 98%) as a pure (^1H NMR, 400 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 1726; ^1H NMR (CD_2Cl_2, 400 MHz) δ 0.40 (s, 3 H), 0.41 (s, 3 H), 0.55-0.72 (m, 6 H), 0.72-1.18 (m, 2[illegible] H), 1.18-1.50 [m, including singlets at δ 1.32 (3 H) and δ 1.42 (3 H), 12 H in all], 1.60-1.75 (m, 3 H), 1.75-1.95 (m, 1 H), 2.00-2.42 (m, 3 H), 2.42-2.60 (m, 2 H), 3.35-3.40 (br s, 1 H), 3.65-3.78 (m,

2 H), 3.78-3.90 (m, 1 H), 4.02-4.15 (m, 1 H), 4.25-4.35 (m, 1 H), 7.30-7.50 (m, 9 H), 7.50-7.63 (m, 2 H), 7.63-7.75 (m, 4 H); ^{13}C NMR -3.06 (q'), -2.62(q'), 5.28 (t'), 7.19 (q'), 12.73 (q'), 19.51 (s'), 20.11 (q'), 26.21 (t'), 27.12 (q'), 28.23 (d'), 30.54 (q'), 32.36 (d'), 32.47 (t'), 34.77 (t'), 36.45 (d'), 37.79 (t'), 39.89 (t'), 40.19 (t'), 51.12 (d'), 54.97 (d'), 60.18 (t'), 65.98 (d'), 66.64 (s'), 69.19 (d'), 69.65 (d'), 98.69 (s'), 128.09 (d'), 128.38 (d'), 129.63 (d'), 130.02 (d'), 134.25 (d'), 134.44 (s'), 135.97 (d'), 138.03 (s'), 207.27 (s'); FABMS *m/z* calcd for $C_{51}H_{76}O_6Si_3$ (M + H) 869, found 869. Anal. calcd for $C_{51}H_{76}O_6Si_3$: C, 70.46; H, 8.81. Found: C, 70.76; H, 9.06.

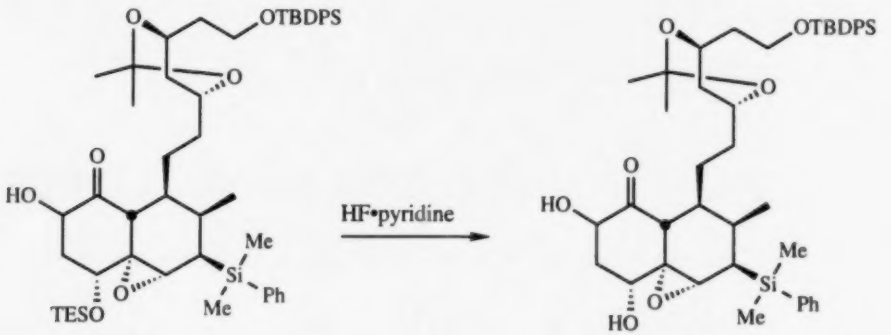
[2R-[2α,3α,4α(4R*,6S*),4aα,8β]]-4-[2-[6-[2-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]ethyl]-2,2-dimethyl-1,3-dioxan-4-yl]ethyl]-2-(dimethylphenylsilyl)hexahydro-6-hydroxy-3-methyl-8-[(triethylsilyl)oxy]-3*H*-naphth[1,8a-b]oxiren-5(6*H*)-one (29).



28 29

Ketone **28** (0.125 g, 0.144 mmol) in THF (0.85 mL plus 2 x 0.1 mL as rinses) was added dropwise (over *ca.* 5 min) to a stirred and cooled (-78 °C) solution of $(Me_3Si)_2NLi$ (0.5 M in PhMe, 0.46 mL, 0.23 mmol) in THF (4.3 mL). Stirring was continued for 30 min, and then 2-(phenylsulfonyl)-3-(*p*-nitrophenyl)oxaziridine[48] (60 mg, 0.23 mmol) in THF (0.75 mL) was added over *ca.* 5 min. Stirring was continued for 30 min and then AcOH (0.165 mL, 2.88 mmol) was added. The cold bath was removed and the mixture was allowed to attain room temperature (30-40 min). The mixture was concentrated at room temperature to 5-10 mL, and the residue was dissolved in EtOAc (50 mL), washed with saturated aqueous NH_4Cl (1 x 50 mL), water (2 x 20 mL) and brine (1 x 20 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1 x 20 cm), using first 1:9 EtOAc-CH_2Cl_2, then 1:4 EtOAc-CH_2Cl_2, and finally 35:65 EtOAc-CH_2Cl_2, gave **29** (86 mg, 67%) as a pure (^1H NMR,400 MHz), colorless oil: ^1H NMR (CD_2Cl_2, 400 MHz) δ 0.42 (s, 3 H), 0.43 (s, 3 H), 0.55-0.75 (m, 6 H), 0.75-1.56 [m, including singlets at δ 1.05 (9 H), δ 1.32 (3 H), δ 1.42 (3 H), 31 H in all], 1.60-2.55 (m, 9 H), 2.70-2.82 (m, 1 H), 3.10-3.22 (d, J = 11 Hz, 1 H), 3.30-3.40 (br s, 1 H), 3.63-3.97 (m, 3 H), 4.00-4.20 (m, 2 H), 4.50-4.65 (m, 1 H), 7.30-7.50 (m, 9 H), 7.50-7.62 (m, 2 H),7.62-7.78 (m, 4 H); FABMS *m/z* calcd for $C_{50}H_{73}O_7Si_3$ (M - CH_3) 869, found 869.

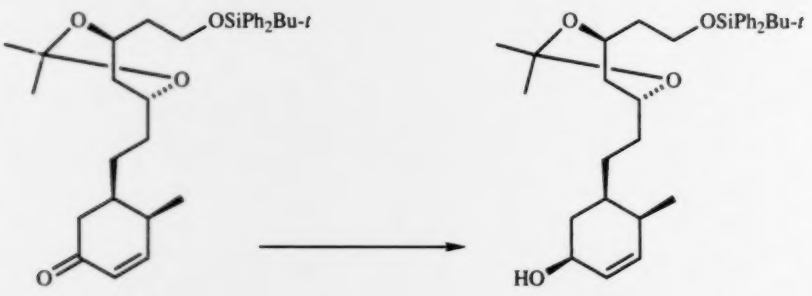
[2R-[2α,3α,4α(4R*,6S*),4aα,8β]]-4-[2-[6-[2-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]ethyl]-2,2-dimethyl-1,3-dioxan-4-yl]ethyl]-2-(dimethylphenylsilyl)hexahydro-6,8-dihydroxy-3-methyl-3*H*-naphth[1,8a-b]oxiren-5(6*H*)-one (25).



HF•pyridine (0.51 mL, 70% HF in pyridine) was added to a stirred and cooled (-78 °C) solution of **29** (1.267 g, 1.431 mmol) in THF (50 mL) contained in a plastic vessel. The mixture was stirred at -78 °C for 10 min and the cold bath was then removed. Stirring was continued for 1.5 h. (tlc control, silica, 3:2 EtOAc-hexane). Additional HF•pyridine (0.51 mL, 70% HF in pyridine) was added to the solution, again at -78 °C and, after 10 min, the cold bath was removed The mixture was stirred for 1 h and then poured into cold (0 °C) EtOAc (200 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (2 x 40 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 x 20 cm), using first 3:7 EtOAc-hexane and subsequently 4:6, 1:1 and finally 3:2 EtOAc-hexane, gave **25**

(0.913 g, 82%) as a pure (^{1}H NMR, 400 MHz), colorless oil whose ^{1}H NMR spectrum was the same as that obtained by Chengzhi Zhang.[45]

[1S-[1α,4α,5α(4S*,6R*)]]-5-[2-[6-[2-[[(1,1-dimethylethyl)diphenylsilyl]oxy]ethyl]-2,2-dimethyl-1,3-dioxan-4-yl]ethyl]-4-methyl-2-cyclohexen-1-ol (37).



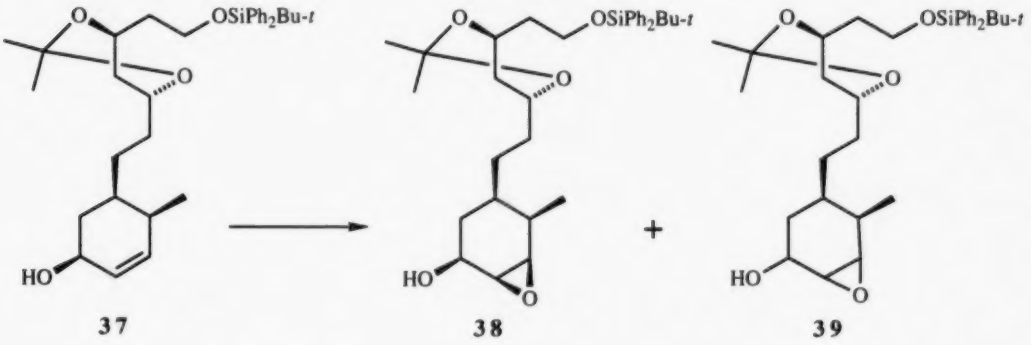
17 **37**

DIBAL (1.9 mL, 1 M in CH_2Cl_2, 1.88 mmol) was added dropwise to a stirred and cooled (0 °C) solution of enone **17** (689 mg, 1.25 mmol) in dry CH_2Cl_2 (135 mL). The mixture was then transferred dropwise, using a cannula, into stirred and cooled (-78 °C) 1:2 MeOH:CH_2Cl_2 (250 mL). The cooling bath was removed and water (100 mL) was added while the mixture was still cold (*ca.* 0 °C). The mixture was stirred vigorously for 1 h to allow a precipitate to form. The precipitate was filtered off and the layers were separated. The organic layer was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (4 x 25 cm), using first 1:4 EtOAc-hexane and then 3:7 EtOAc-hexane, gave

37 (571 mg, 82%) as a colorless oil, which was a mixture of two diastereoisomers (^{1}H NMR, 400 MHz): FTIR (CH_2Cl_2 cast) 3600-3100, 1111 cm^{-1}; ^{1}H NMR (acetone-d_6, 400 MHz) δ 0.80* (d, *J* = 7.2 Hz, 0.24 H), 0.84 (d, *J* = 7.1 Hz, 3 H), 0.98-1.32 [m, including singlets at δ 1.05 (9 H) and δ 1.30 (3 H), 15 H in all], 1.32-1.57 [m, including a singlet at δ 1.42 (3 H), 7 H in all], 1.57-1.77 (m, 4 H), 1.9* (br s, 0.08 H), 2.10-2.20 (m, 1 H), 3.30-3.50* (m, 0.39 H), 3.65 (d, *J* = 6.1 Hz, 0.6 H), 3.68-3.78 (m, 1 H), 3.78-3.90 (m, 2 H), 4.05* (br s, 0.15 H), 4.10-4.22 (m, 2 H), 5.50-5.80 (m, 2 H), 7.40-7.50 (m, 6 H), 7.68-7.78 (m, 4 H); ^{13}C NMR (acetone-d_6, 100.6 MHz) δ 13.58* (d'), 14.37 (d'), 19.56 (s'), 20.13 (d'), 27.15 (q'), 27.90* (t'), 29.24 (t'), 30.65 (q'), 32.51* (q'), 32.62 (q'), 32.93* (q'), 34.17* (t'), 34.48 (t'), 34.51 (t'), 34.84* (t'), 36.29 (q'), 38.00 (t'), 40.06 (t'), 60.30 (t'), 64.17* (d'), 66.05 (d'), 68.25 (d'), 69.58 (d'), 98.63 (s'), 128.38 (d'), 128.87* (d'), 130.36 (d'), 132.14 (d'), 134.37 (s'), 134.37* (d'), 136.06 (d'), 136.24 (d'); exact mass *m/z* calcd for $C_{32}H_{45}O_4Si$ (M - CH_3) 521.3087, found 521.3077. The starred ^{13}C signals are due to the C(1) epimer, which could not be separated.

[1S-[1α,2β,4β(4S*,6R*),5β,6α]]-4-[2-[6-[2-[[(1,1-dimethylethyl)diphenylsilyl]oxy]ethyl]-2,2-dimethyl-1,3-dioxan-4-yl]ethyl]-5-methyl-7-oxabicyclo[4.1.0]-heptan-2-ol (38) and [1R-[1α,2α,4α(4R*,6S*),5α,6α]]-4-[2-[6-[2-[[(1,1-dimethylethyl)diphenylsilyl]oxy]ethyl]-2,2-dimethyl-1,3-

dioxan-4-yl]ethyl]-5-methyl-7-oxabicyclo[4.1.0]heptan-2-ol (39).



37 **38** **39**

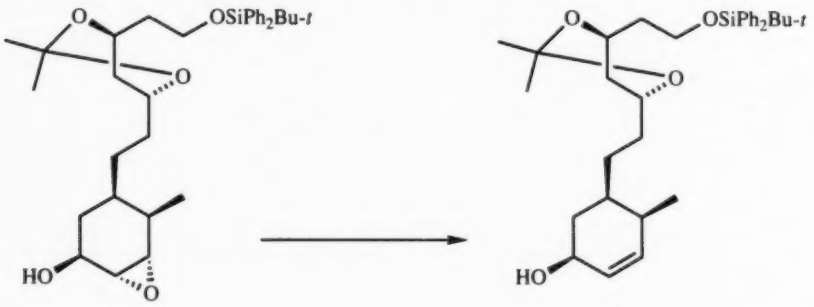
m-CPBA (346 mg, 2.00 mmol) was diluted with dry CH_2Cl_2 (68 mL) and added dropwise to a stirred and cooled (-78 °C) mixture of **37** (539 mg, 1.00 mmol) and $NaHCO_3$ (422 mg, 3.98 mmol) in dry CH_2Cl_2 (68 mL). The mixture was stirred at -78 °C for 2 h, and then the cold bath was removed, and the mixture was stirred for 14 h. The mixture was filtered and EtOAc (100 mL) was added. The organic layer was washed with aqueous Na_2SO_3 (10%, 1 x 50 mL), saturated aqueous $NaHCO_3$ (1 x 50 mL), water (1 x 50 mL), and brine (1 x 50 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (4 x 25 cm), using first 3:7 EtOAc-hexane and then 2:3 EtOAc-hexane, gave **38** (358 mg, 64%) as a pure (^1H NMR, 200 MHz), colorless oil and **39** (131 mg, 23%) as a colorless oil which was a mixture of two isomers (^1H NMR, 300 MHz). Compound **38** had: FTIR (CH_2Cl_2 cast) 3600-3200, 1111 cm^{-1}; ^1H NMR (acetone-d_6, 200 MHz) δ 0.90 (d, J = 8 Hz, 3 H), 0.95-1.60 [m, including singlets at δ 1.05 (9 H), δ 1.30 (3 H)

and δ 1.41 (3 H), 25 H in all], 1.60-1.78 (m, 2 H), 2.00-2.10 (m, including acetone, 1 H), 3.10-3.25 (m, 2 H), 3.70-4.00 (m, 4 H), 4.05-4.30 (m, 1 H), 7.38-7.55 (m, 6 H), 7.62-7.78 (m, 4 H); ^{13}C NMR (acetone-d_6, 50.3 MHz) δ 9.55 (d'), 19.62 (s'), 20.17 (d'), 27.21 (q'), 28.21 (t'), 29.32 (q'), 30.68 (q'), 30.83 (t'), 34.91 (t'), 37.48 (q'), 38.03 (t'), 40.13 (t'), 57.63 (d'), 59.15 (d'), 60.42 (t'), 66.18 (d'), 69.60 (d'), 70.14 (d'), 98.70 (s'), 128.44 (d'), 130.42 (d'), 134.47 (s'), 136.12 (d'); exact mass *m/z* calcd for $C_{32}H_{45}O_5Si$ (M - CH_3) 537.3037, found 537.3032.

Compound **39** had: FTIR (CH_2Cl_2 cast) 3600-3200, 1111 cm^{-1}; ^1H NMR (acetone-d_6, 300 MHz) δ 0.80-1.45 [m, including singlets at δ 1.05 (9 H), δ 1.28 (3 H), δ 1.42 (3 H), 24 H in all], 1.45-1.55 (m, 2 H), 1.55-1.80 (m, 2 H), 2.06-2.20 (m, 1 H), 2.90-3.25 (m, 2 H), 3.25-3.45 (m, 1 H), 3.65-3.95 (m, 4 H), 3.95-4.25 (m, 2 H), 7.30-7.50 (m, 6 H), 7.65-7.80 (m, 4 H); ^{13}C NMR (acetone-d_6, 50.3 MHz) δ 10.24* (d'), 11.37 (d'), 20.03 (s'), 20.57 (d'), 27.60 (q'), 27.94 (t'), 29.10* (t'), 30.09 (q'), 31.08 (q'), 31.85* (q'), 32.27 (q'), 32.78 (t'), 32.87* (t'), 35.10 (t'), 38.44 (t'), 40.57 (t'), 55.02 (d'), 57.72* (d'), 59.73* (d'), 60.05 (d'), 60.85 (t'), 64.65 (d'), 66.61 (d'), 66.89* (d'), 70.04 (d'), 99.12 (s'), 128.87 (d'), 130.84 (d'), 134.91 (s'), 136.56 (d'); exact mass *m/z* calcd for $C_{32}H_{45}O_5Si$ (M - CH_3) 537.3037, found 537.3033.

* signals due to a minor isomer.

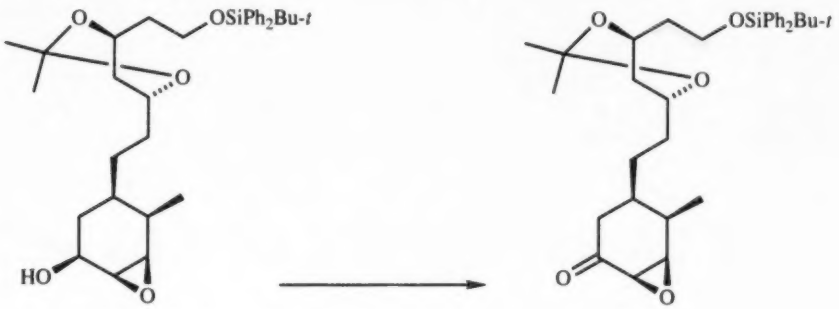
[1S-[1α,4α,5α(4S*,6R*)]]-5-[2-[6-[2-[[(1,1-dimethyl-ethyl)diphenylsilyl]oxy]ethyl]-2,2-dimethyl-1,3-dioxan-4-yl]ethyl]-4-methyl-2-cyclohexen-1-ol (37).



39 **37**

$(EtO)_2P(O)Na$[70] (*ca.* 1 M in THF) was added to Te powder (200 mesh, 20 mg, 0.13 mmol) until all the Te had dissolved. The solution was evaporated with scrupulous protection from air and **39** (36 mg, 0.065 mmol) in EtOH (5 mL plus 2 mL as a rinse) was added with stirring at room temperature. The mixture was stirred for 2 h and then the solvent was evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 1:4 EtOAc-hexane, gave 3 compounds, but the recovery of the desired compound was too small to be useful.

[1R-[1α,4β(4R*,6S*),5β,6α]]-4-[2-[6-[2-[[(1,1-dimethylethyl)diphenylsilyl]oxy]ethyl]-2,2-dimethyl-1,3-dioxan-4-yl]ethyl]-5-methyl-7-oxabicyclo[4.1.0]heptan-2-one (34).

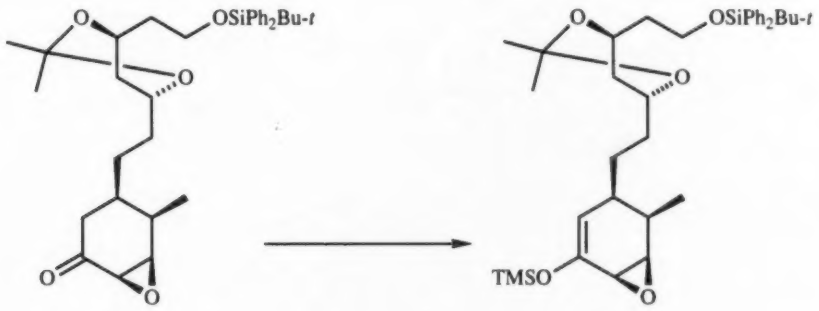


38 **34**

TPAP (21 mg, 0.059 mmol) was added to a stirred and cooled (0 °C) solution of **38** (334 mg, 0.588 mmol), NMO (172 mg, 1.47 mmol), and powdered 4Å molecular sieves (201 mg) in CH_2Cl_2 (18 mL). The cold bath was removed after 1 h and the mixture was then stirred for 4 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 20 cm), using 1:4 EtOAc-hexane, gave **34** (289 mg, 86%) as a pure (^{1}H NMR, 200 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 1718 cm^{-1}; ^{1}H NMR (acetone-d_6, 200 MHz) δ 0.78-1.25 [m, including a singlet at δ 1.05 (9 H), 14 H in all], 1.25-1.57 [m, including singlets at δ 1.30 (3 H) and δ 1.45 (3 H), 10 H in all], 1.57-1.90 (m, 3 H), 1.90-2.10 (m, 1 H), 2.30-2.42 (m, 1 H), 2.42-2.60 (dd, *J* = 14 Hz, 14 Hz, 1 H), 3.10-3.20 (m, 1 H), 3.55-3.65 (m, 1 H), 3.65-3.95 (m, 3 H), 4.10-4.30 (m, 1 H), 7.40-7.55 (m, 6 H), 7.60-7.80 (m, 4 H); ^{13}C NMR (acetone-d_6, 50.3 MHz) δ 9.69 (d'), 19.53 (s'), 20.06 (d'), 27.10 (q'),

28.26 (t'), 29.75 (q'), 30.56 (q'), 34.42 (t'), 37.87 (t'), 38.61 (t'), 40.01 (t'), 41.76 (q'), 55.93 (d'), 60.28 (t'), 63.23 (d'), 65.99 (d'), 69.30 (d'), 98.63 (s'), 128.34 (d'), 130.30 (d'), 134.37 (s'), 136.01 (d'), 206.65 (s'); exact mass *m/z* calcd for $C_{32}H_{43}O_5Si$ (M - CH_3) 535.2880, found 535.2876.

[4S-[4α(1αS*,4β,5β,6α),6α]]-4-[2-[[(1,1-dimethylethyl)diphenylsilyl]oxy]ethyl]-2,2-dimethyl-6-[2-[5-methyl-2-[(trimethylsilyl)oxy]-7-oxabicyclo[4.1.0]hept-2-en-4-yl]ethyl]-1,3-dioxolane (40).

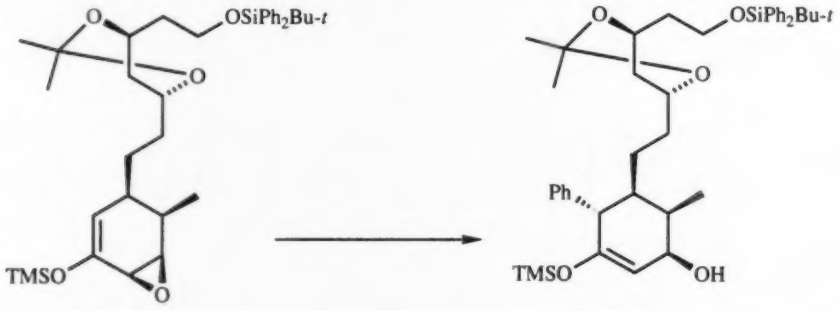


34 **40**

A 1:1 mixture of Me_3SiCl and Et_3N (28 μL, 0.28 mmol of Me_3SiCl) was added to a stirred and cooled (-78 °C) solution of **34** (268 mg, 0.487 mmol) in THF (23 mL). $(Me_3Si)_2NLi$ (0.5 M in PhMe, 1.95 mL, 0.974 mmol) was added dropwise. The solution was stirred at -78 °C for 4 h after the addition. The cold bath was then removed and the mixture was stirred for 13 h. Et_2O (50 mL) was added and the resulting precipitate was removed by filtration through Celite (3 x 6

cm). Evaporation of the filtrate afforded **40** as a colorless oil, sufficiently pure for the next step: ^{1}H NMR (acetone-d_6, 300 MHz) δ 0.15-0.30, (TMS signal, 9 H), 5.1 (m, olefin signal, 1 H).

[1R-[1α,4β,5α(4R*,6S*),6α]]-5-[2-[6-[2-[[(1,1-dimethylethyl)diphenylsilyl]oxy]ethyl]-2,2-dimethyl-1,3-dioxan-4-yl]ethyl]-6-methyl-3-[(trimethylsilyl)oxy]-4-phenyl-2-cyclohexene-1-ol (41).



40 41

(a) Formation of PhMgBr. PhBr (1.18 mL) was added dropwise to a stirred and refluxing mixture of freshly ground (mortar and pestle) Mg (233 mg, 11.22 mmol) in dry Et_2O (18 mL). After addition of PhBr the solution was refluxed for 45 min, by which time all the Mg had dissolved.

(b) Purification of CuCN. CuCN (15 g) was stirred with water (60 mL) for 19 h. The mixture was filtered and the solid was washed with water (3 x 50 mL) and absolute EtOH (2 x 20 mL). The resulting CuCN was transferred to a round bottomed flask with PhMe, and water was removed by evaporation with PhMe (3

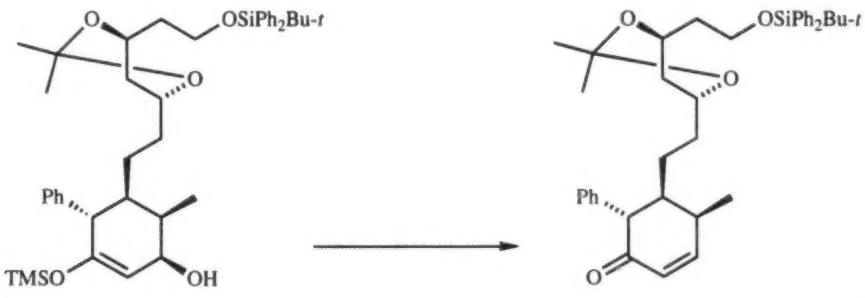
x 50 mL). The solid was kept under diffusion pump vacuum for 15 h.

(c) Formation of the Cuprate. The phenylmagnesium bromide solution was added to a stirred and cooled (-42 °C) mixture of CuCN (1.01 g, 11.2 mmol) (weighed out in glove bag) in Et_2O (18 mL). The mixture was stirred for 45 min, by which stage a yellow color had appeared. (If the mixture is white it should be warmed slightly until the yellow color develops.)

(d) Conjugate addition. PhCuCNMgBr (*ca.* 36 mL, *ca.* 11 mmol in Et_2O) (at -42 °C) was added through a cannula to a stirred and cooled (-78 °C) solution of **40** (268 mg, 0.431 mmol) in Et_2O (18 mL). The mixture was stirred at -78 °C for 2 h and the cold bath was then removed. Stirring was continued for 18 h. Et_2O (100 mL) was added and the organic layer was washed with saturated aqueous NH_4Cl (1 x 50 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 x 20 cm), using first 1:9 EtOAc-hexane and then 1:4 EtOAc-hexane, gave **41** (304 mg, 89% over 2 steps) as a pure (^1H NMR, 400 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 3600-3200, 3100-3000, 1659 cm^{-1}; ^1H NMR (acetone-d_6, 400 MHz) δ 0.0 (s, 9 H), 0.80-1.50 [m, including a doublet at δ 0.90 (*J* = 7 Hz, 3 H) and singlets at δ 1.05 (9 H), δ 1.17 (3 H), δ 1.32 (3 H), 24 H in all], 1.55-1.70 (m, 2 H), 1.75-1.85 (m, 1 H), 2.07-2.20 (m, 1 H), 2.90-3.05 (m, 1 H), 3.60-3.75 (m, 3 H), 3.75-3.90 (m, 1 H), 4.00-4.15 (m, 1 H), 4.50-4.60 (m, 1 H), 4.85-4.95 (m, 1 H), 7.10-7.22 (m, 3 H), 7.22-7.30 (m, 2

H), 7.30-7.50 (m, 6 H), 7.60-7.75 (m, 4 H); ^{13}C NMR (acetone-d_6, 100.6 MHz) δ 0.20 (q'), 19.55 (s'), 19.99 (d'), 25.37 (t'), 27.16 (q'), 30.53 (two overlapping signals, d', q'), 34.70 (t'), 35.09 (d'), 37.99 (t'), 40.01 (t'), 50.94 (q'), 60.23 (t'), 65.92 (d'), 68.87 (d'), 69.80 (two overlapping signals, d', q'), 98.56 (s'), 109.45 (d'), 126.70 (d'), 128.35 (d'), 128.39 (d'), 129.70 (d'), 130.34 (d'), 134.37 (s'), 136.05 (d'), 143.62 (s'), 151.98 (s'); exact mass *m/z* calcd for $C_{41}H_{57}O_5Si_2$ (M - CH_3) 685.3745, found 685.3749.

[4S-[4α,5α(4S*,6R*),6β]]-5-[2-[6-[2-[[(1,1-dimethylethyl)diphenylsilyl]oxy]ethyl]-2,2-dimethyl-1,3-dioxan-4-yl]ethyl]-4-methyl-6-phenyl-2-cyclohexene-1-one (33).

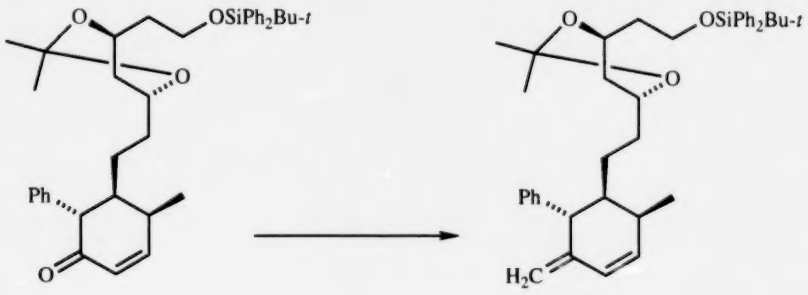


41 **33**

Pyridine (29 μL, 0.22 mmol) was added to a stirred and cooled (-78 °C) solution of **41** (*ca.* 18 mg, 0.026 mmol) in dry CH_2Cl_2 (1 mL). $MeSO_2Cl$ (15.1 μL, 0.196 mmol) was then added and the mixture was stirred at -78 °C for 30 min. The cold bath was then removed and stirring was continued for 12 h. Et_2O (25 mL) was added and the organic layer was washed with

water (25 mL), 10% aqueous $CuSO_4$ (25 mL) and saturated aqueous $NaHCO_3$ (25 mL). The organic extract was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 20 cm), using first 1:9 EtOAc-hexane, then 1:4, and finally 3:7 EtOAc-hexane, gave **33** (14 mg, 87%) as a pure (^1H NMR, 360 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 1678 cm^{-1}; ^1H NMR (acetone-d_6, 360 MHz) δ 0.90-1.50 [m, including singlets at δ 1.02 (9 H), δ 1.20 (3 H), δ 1.35 (3 H), and a doublet at δ 1.12 (J = 7.2 Hz, 3 H), 23 H in all], 1.55-1.70 (m, 2 H), 2.35-2.55 (m, 1 H), 2.70-2.82 (m, 2 H), 3.50-3.55 (d, J = 11.4 Hz, 1 H), 3.65-3.78 (m, 2 H), 3.78-3.90 (m, 1 H), 4.00-4.20 (m, 1 H), 5.90-6.00 (dd, J = 10.0, 1.5 Hz, 1 H) 7.05-7.35 (m, 6 H), 7.35-7.50 (m, 6 H), 7.65-7.75 (m, 4 H); ^{13}C NMR (acetone-d_6, 50.3 MHz) δ 12.95 (d'), 19.62 (s'), 20.14 (d'), 25.60 (t'), 27.20 (q'), 30.62 (q'), 32.06 (d'), 33.73 (t'), 38.06 (t'), 40.10 (t'), 43.29 (q'), 56.03 (q'), 60.37 (t'), 66.04 (d'), 68.88 (d'), 98.69 (s'), 127.11 (d'), 128.45 (d'), 128.59 (d'), 128.81 (d'), 130.02 (d'), 130.43 (d'), 134.51 (s'), 136.13 (d'), 140.23 (s'), 155.50 (d'), 199.05 (s'); exact mass m/z calcd for $C_{38}H_{47}O_4Si$ (M - CH_3) 595.3243, found 595.3235.

[4R-[4α(1αS*,2α,6β),6α]]-4-[2-(2-methyl-5-methylene-6-phenyl-3-cyclohexen-1-yl)ethyl]-6-[2-[[(1,1-dimethylethyl)diphenylsilyl]oxy]ethyl]-2,2-dimethyl-1,3-dioxolane (46).



33 **46**

Tebbe reagent (0.5 M in PhMe, 0.70 mL, 0.35 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of **33** (213 mg, 0.349 mmol) in dry THF (61 mL). After the addition the cold bath was removed and the mixture was stirred for 30 min. Et_2O (100 mL) was added and then NaOH (0.1 N) was added dropwise until no more gas evolution was seen. Water (20 mL) was added and the organic layer was dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (2.5 x 20 cm), using 5:95 EtOAc-hexane, gave **46** (178 mg, 81%) as a pure (^1H NMR, 200 MHz), colorless oil: FTIR (CH_2Cl_2 cast) unexceptional; ^1H NMR (acetone-d_6, 200 MHz) δ 0.80-1.20 [m, including a doublet at δ 0.95 (J = 7 Hz, 3 H) and a singlet at δ 1.05 (9 H), 14 H in all], 1.20-1.55 (m, including singlets at δ 1.28 (3 H) and δ 1.42 (3 H), 10 H in all], 1.55-1.75 (m, 2 H), 1.85-2.02 (m, 1 H), 2.20-2.40 (m, 1 H), 3.50-

3.60 (m, 1 H), 3.62-3.95 (m, 3 H), 4.02-4.25 (m, 1 H), 4.50-4.60 (br s, 1 H), 4.95-5.05 (br s, 1 H), 5.65-5.80 (m, 1 H), 6.20-6.35 (m, 1 H), 7.10-7.35 (m, 5 H), 7.35-7.50 (m, 6 H), 7.65-7.78 (m, 4 H); ^{13}C NMR (acetone-d_6, 100.6 MHz) δ 16.13 (d'), 19.68 (s'), 20.23 (d'), 24.31 (t'), 27.26 (q'), 30.74 (two overlapping signals, d', q'), 34.76 (t'), 38.22 (t'), 40.21 (t'), 43.84 (q'), 48.95 (q'), 60.48 (t'), 66.19 (d'), 69.61 (d'), 98.74 (s'), 115.10 (t'), 126.70 (d'), 128.48 (d'), 128.79 (d'), 129.19 (d'), 129.52 (d'), 130.45 (d'), 134.58 (s'), 135.47 (d'), 136.20 (d'), 144.72 (s'), 145.91 (s'); exact mass *m/z* calcd for $C_{39}H_{49}O_3Si$ (M - CH_3) 593.3451, found 593.3451.

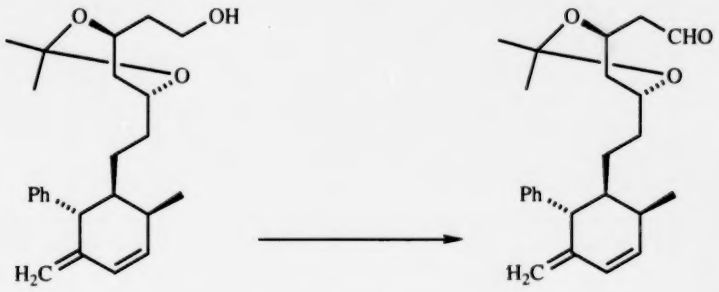
[4S-[4α,6α(1αR*,2α,6β)]]-2-[6-[2-(2-methyl-5-methylene-6-phenyl-3-cyclohexen-1-yl)ethyl]-2,2-dimethyl-1,3-dioxan-4-yl]ethanol (47).

46 **47**

TBAF (1 M in THF, 0.77 mL, 0.77 mmol) was added to a stirred and cooled (-78 °C) solution of **46** (171 mg, 0.273 mmol) in dry THF (36 mL). The cold bath was removed after 30

min and the mixture was stirred for 16 h. Et_2O (100 mL) and water (100 mL) were added and the organic phase was dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 25 cm), using 3:7 EtOAc-hexane, gave **47** (99 mg, 97%) as a pure (^1H NMR, 200 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 3600-3200 cm^{-1}; ^1H NMR (acetone-d_6, 200 MHz) δ 0.80-1.70 [m, including a doublet at δ 0.95 (J = 7 Hz, 3 H) and singlets at δ 1.25 (3 H) and δ 1.40 (3 H), 17 H in all], 1.85-2.00 (m, 1 H), 2.20-2.38 (m, 1 H), 3.30-3.40 (dd, J = 4.8, 4.8 Hz, 1 H), 3.50-3.70 (m, 3 H), 3.70-3.90 (m, 1 H), 3.95-4.12 (m, 1 H), 4.50-4.58 (br s, 1 H), 4.95-5.05 (br s, 1 H), 5.65-5.75 (m, 1 H), 6.20-6.35 (dd, J = 10.0, 2.5 Hz, 1 H), 7.10-7.35 (m, 5 H); ^{13}C NMR (acetone-d_6, 50.3 MHz) δ 16.06 (d'), 20.20 (d'), 24.32 (t'), 30.75 (two overlapping signals, d', q'), 34.76 (t'), 38.15 (t'), 40.32 (t'), 43.82 (q'), 48.98 (q'), 59.05 (t'), 67.51 (d'), 69.62 (d'), 98.77 (s'), 115.05 (t'), 126.72 (d'), 128.82 (d'), 129.22 (d'), 129.53 (d'), 135.52 (d'), 144.76 (s'), 146.02 (s'); exact mass m/z calcd for $C_{23}H_{31}O_3$ (M - CH_3) 355.2273, found 355.2279.

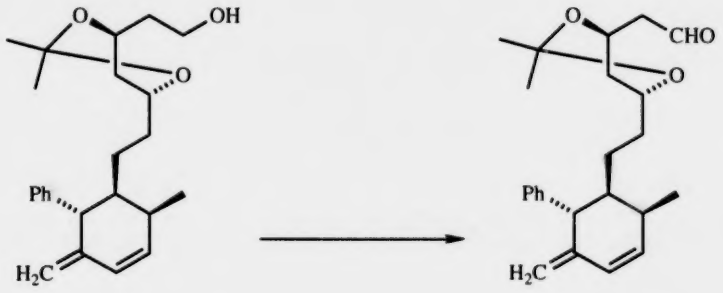
[4R-[4α,6α(1αS*,2α,6β)]]-[6-[2-(2-methyl-5-methylene-6-phenyl-3-cyclohexen-1-yl)ethyl]-2,2-dimethyl-1,3-dioxan-4-yl]ethanal (48).



47 **48**

A portion (*ca.* 1 mL) of a mixture of CrO_3 (200 mg), pyridine (323 μL), and CH_2Cl_2 (3.5 mL) was added to alcohol **47** (*ca.* 12.2 mg, 0.0329 mmol) in CH_2Cl_2 (2 mL) and the mixture was stirred at room temperature for 10 min. The mixture was filtered through silica gel (3 x 5 cm) with EtOAc and the filtrate was evaporated. Flash chromatography of the residue over silica gel (0.75 cm x 10 cm), using 3:7 EtOAc-hexane, gave **48** (*ca.* 7.7 mg, 63%) as a pure (^{1}H NMR, 300 MHz), colorless oil, whose ^{1}H NMR spectrum was identical to that measured in the next experiment.

[4R-[4α,6α(1αS*,2α,6β)]]-[6-[2-(2-methyl-5-methylene-6-phenyl-3-cyclohexen-1-yl)ethyl]-2,2-dimethyl-1,3-dioxan-4-yl]]ethanal (48).

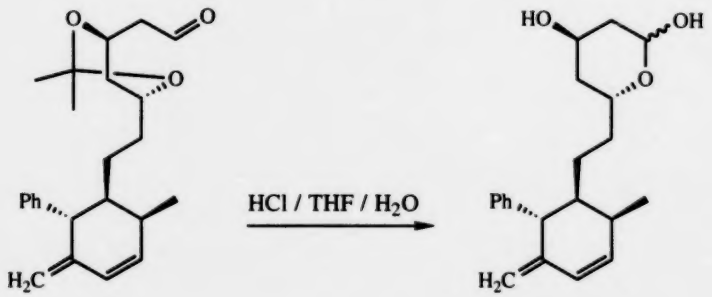


47 **48**

DMSO (37 μL, 0.52 mmol) was added to a stirred and cooled (-78 °C) solution of $(COCl)_2$ (30 μL, 0.34 mmol) in CH_2Cl_2 (3.7 mL). After 10 min, alcohol **47** (*ca.* 28.7 mg, 0.077 mmol) in CH_2Cl_2 (3.7 mL) (plus 1 x 1.7 mL as a rinse) was added. The mixture was stirred for 20 min and Et_3N (0.19 mL) was added. After 10 min the cold bath was removed and then the mixture was stirred for an additional 20 min. Water (8 drops) and Et_2O (50 mL) were added. The organic solution was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 3:7 EtOAc-hexane, gave **48** (*ca.* 27.4 mg, 96%) as a pure (^1H NMR, 400 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 2871, 2726, 1726 cm^{-1}; ^1H NMR (acetone-d_6, 400 MHz) δ 0.80-1.65 [m, including a doublet at δ 0.96 (*J* = 7.3 Hz, 3 H) and singlets at δ 1.28 (3 H) and δ 1.43 (3 H), 15 H in all], 1.85-2.0 (m, 1 H), 2.25-2.38 (m, 1 H), 2.38-2.50 (m, 2 H), 3.50-3.60 (d, *J* = 7 Hz, 1 H), 3.80-3.90

(m, 1 H), 4.40-4.60 (m and br s at δ 4.55, 2 H), 4.95-5.05 (br s, 1 H), 5.65-5.75 (m, 1 H), 6.20-6.30 (dd, *J* = 9.8, 2.1 Hz, 1 H), 7.15-7.23 (m, 3 H), 7.23-7.35 (m, 2 H), 9.65-9.73 (br s, 1 H); ^{13}C NMR (acetone-d_6, 100.6 MHz) δ 16.03 (d'), 20.08 (d'), 24.25 (t'), 30.48 (d'), 30.76 (q'), 34.59 (t'), 37.57 (t'), 43.75 (q'), 48.92 (q'), 50.48 (t'), 65.49 (d'), 69.46 (d'), 99.10 (s'), 115.09 (t'), 126.78 (d'), 128.87 (d'), 129.26 (d'), 129.54 (d'), 135.52 (d'), 144.76 (s'), 146.04 (s'), 201.42 (d'); exact mass *m/z* calcd for $C_{24}H_{32}O_3$ 368.2351, found 368.2344.

[2R-[2α,4β,6α(1αS*,2α,6β)]]- and [2S-[2α,4α,6β(1αR*,2α,6β)]]-6-[2-(2-methyl-5-methylene-6-phenyl-3-cyclohexen-1-yl)ethyl]tetrahydro-4-hydroxy-2*H*-pyran-2-ol (49).

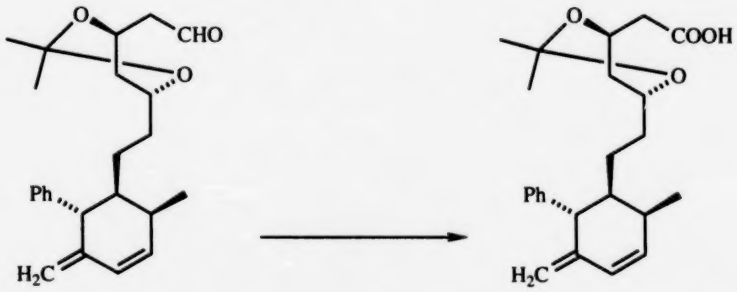


48 **49**

Hydrochloric acid (2 M, 15 drops) was added to a stirred mixture of **48** (*ca.* 4.9 mg, 0.0133 mmol), water (5 drops) and THF (2 mL). The mixture was stirred at room temperature for 7 h. Et_2O (30 mL) was added and the organic phase was washed

with saturated aqueous $NaHCO_3$ (20 mL) and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (0.75 x 10 cm), using 1:1 EtOAc-hexane, gave **49** (*ca.* 3.1 mg, 70%) as a colorless oil which contained trace impuritities (^{1}H NMR, 400 MHz): ^{1}H NMR (acetone-d_6, 300 MHz) δ 0.80-2.0 [m, including a doublet at δ 0.98 (J = 8 Hz, 3 H), 13 H in all] 2.20-2.40 (m, 1 H), 3.50-3.64 (m, 1 H), 3.64-4.10 (m, 2 H), 4.10-4.24 (m, 1 H), 4.48-4.62 (m, 1 H), 4.95-5.19 (m, 2 H), 5.60-5.80 (m, 1 H), 6.20-6.35 (m, 1 H), 7.10-7.23 (m, 3 H), 7.23-7.33 (m, 2 H).

[4R-[4α,6α(1αS*,2α,6β)]]-[6-[2-(2-methyl-5-methylene-6-phenyl-3-cyclohexen-1-yl)ethyl]-2,2-dimethyl-1,3-dioxan-4-yl]ethanoic acid (54).

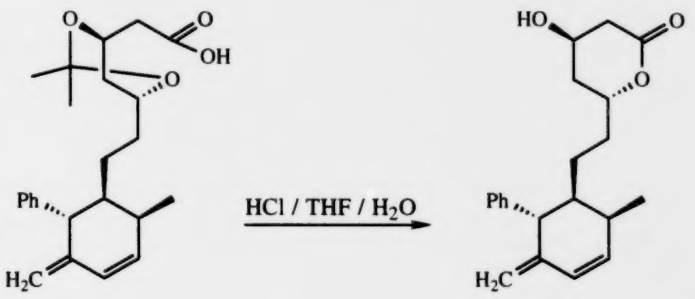


48 **54**

$NaClO_2 \bullet 2H_2O$ (1 g) and NaH_2PO_4 (1 g) were added to water (10 mL) just prior to use. An aliquot (0.41 mL) of this oxidizing solution was added to a stirred and cooled (0 °C) solution of aldehyde **48** (19 mg, 0.052 mmol) in *t*-BuOH (2.1 mL) containing 2-methyl-2-butene (0.52 mL). The cold bath

was removed after 10 min and the mixture was stirred for 1 h. Saturated aqueous NH_4Cl (20 drops) and Et_2O (25 mL) were added. The organic layer was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 20 cm), using first EtOAc and then 2:3 MeOH-EtOAc, gave **54** (*ca.* 18.7 mg, 94%) as a pure (^1H NMR, 400 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 3600-2400, 1710 cm^{-1}; ^1H NMR (acetone-d_6, 400 MHz) δ 0.90-1.55 [m, including a doublet at δ 0.95 (J = 7.3 Hz, 3 H) and singlets at δ 1.25 (3 H) and δ 1.40 (3 H), 15 H in all], 1.55-1.65 (m, 1 H), 1.85-2.0 (m, 1 H), 2.25-2.45 (m, 3 H), 3.50-3.60 (br d, J = 6.9 Hz, 1 H), 3.75-3.90 (m, 1 H), 4.20-4.35 (m, 1 H), 4.45-4.60 (br s, 1 H), 4.95-5.05 (br s, 1 H), 5.65-5.75 (m, 1 H), 6.20-6.30 (dd, J = 9.8, 2.0 Hz, 1 H), 7.10-7.20 (m, 3 H), 7.20-7.35 (m, 2 H); ^{13}C NMR (acetone-d_6, 100.6 MHz) δ 16.09 (d'), 20.21 (d'), 24.32 (t'), 30.61 (q'), 30.76 (d'), 34.70 (t'), 37.69 (t'), 42.40 (t'), 43.75 (q'), 48.94 (q'), 67.04 (d'), 69.47 (d'), 99.00 (s'), 115.11 (t'), 126.76 (d'), 128.86 (d'), 129.26 (d'), 129.54 (d'), 135.56 (d'), 144.78 (s'), 146.05 (s'), 172-174 (br s'); exact mass m/z calcd for $C_{23}H_{29}O_4$ (M - CH_3) 369.2066, found 369.2046.

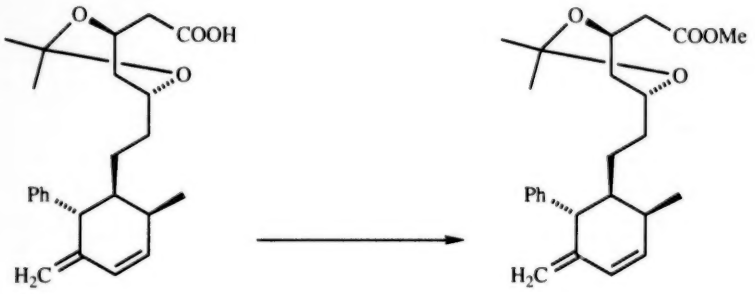
[4R-trans-[1αS*,2α,6β]]-6-[2-(2-methyl-5-methylene-6-phenyl-3-cyclohexen-1-yl)ethyl]tetrahydro-4-hydroxy-2*H*-pyran-2-one (18).



54 **18**

HCl (2 M, 1.1 mL) was added to a stirred mixture of **54** (*ca.* 21.4 mg, 0.056 mmol), water (0.5 mL), and THF (8 mL), and stirring at room temperature was continued for 7 h. Et_2O (30 mL) was added and the organic layer was washed with saturated aqueous $NaHCO_3$ (20 mL), and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (0.75 x 10 cm), using 1:1 EtOAc-hexane, gave **18** (*ca.* 2.3 mg, 12%) as a pure (^1H NMR, 360 MHz), colorless oil, identical with material obtained subsequently (^1H NMR, 400 MHz) by a different method (see later).

Methyl [4R-[4α,6α[1αS*,2α,6β]]-[6-[2-(2-methyl-5-methylene-6-phenyl-3-cyclohexen-1-yl)ethyl]-2,2-dimethyl-1,3-dioxan-4-yl]ethanoate (55).

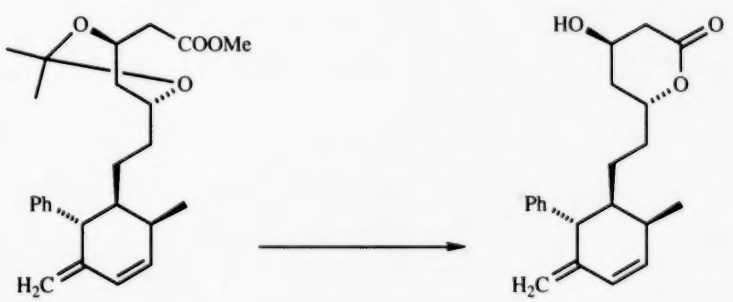


54 **55**

Ethereal diazomethane (0.15 M, 1 mL) was added to a stirred solution of **54** (*ca.* 2.3 mg, 0.006 mmol) in Et_2O (1 mL). More ethereal CH_2N_2 (*ca.* 0.15 M) was added until all the starting material had reacted (tlc control, silica, 5:95 MeOH-EtOAc). Evaporation of the solvent and flash chromatography of the residue over silica gel (0.5 x 6 cm), using 1:9 EtOAc-hexane, gave **55** (*ca.* 1.9 mg, 79%) as a pure (^{1}H NMR, 300 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 1741 cm^{-1}; ^{1}H NMR (acetone-d_6, 400 MHz) δ 0.90-1.60 [m, including a doublet at δ 0.95 (J = 7.3 Hz, 3 H) and singlets at δ 1.25 (3 H) and δ 1.40 (3 H), 15 H in all], 1.85-2.00 (m, 1 H), 2.25-2.35 (m, 1 H), 2.35-2.45 (d, J = 6.4 Hz, 2 H), 3.50-3.65 [m, including a singlet at δ 3.60 (3 H), 4 H in all], 3.75-3.90 (m, 1 H), 4.20-4.35 (m, 1 H), 4.50-4.60 (br s, 1 H), 4.95-5.05 (br s, 1 H), 5.65-5.75 (m, 1 H), 6.20-6.30 (dd, J = 9.9, 2.2 Hz, (1 H)), 7.10-7.23 (m, 3 H), 7.23-7.35 (m, 2 H); ^{13}C

NMR (acetone-d_6, 100.6 MHz) δ 16.03 (d'), 20.04 (d'), 24.26 (t'), 30.52 (q'), 30.77 (d'), 34.64 (t'), 37.45 (t'), 41.82 (t'), 43.77 (q'), 48.94 (q'), 51.53 (q'), 66.79 (d'), 69.44 (d'), 99.05 (s'), 115.08 (t'), 126.78 (d'), 128.87 (d'), 129.27 (d'), 129.55 (d'), 135.55 (d'), 144.80 (s'), 146.00 (s'), 171.54 (s'); exact mass *m/z* calcd for $C_{25}H_{34}O_4$ 398.2457, found 398.2451.

[4R-trans-[1αS*,2α,6β]]-6-[2-(2-methyl-5-methylene-6-phenyl-3-cyclohexen-1-yl)ethyl]tetrahydro-4-hydroxy-2*H*-pyran-2-one (18).



55 **18**

PhH (4.05 mL) was added to **55** (*ca.* 7.7 mg, 0.020 mmol) and TsOH•H_2O (*ca.* 3.7 mg, 0.020 mmol). The mixture was stirred at room temperature for 6 h. $NaHCO_3$ (5 mg) was added followed by EtOAc (25 mL) and water (10 mL). The mixture was stirred briefly and the organic layer was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 1:1 EtOAc-hexane, gave **18** (*ca.* 3.8 mg, 60%) as a pure (^{1}H NMR, 300 MHz), colorless oil: FTIR (CH_2Cl_2

cast) 3600-3200, 1709 cm^{-1}; ^1H NMR (acetone-d_6, 400 MHz) δ 0.80-1.80 [m, including a doublet at δ 1.0 (J = 7.3 Hz, 3 H), 9 H in all], 1.80-2.02 (m, 2 H), 2.25-2.40 (m, 1 H), 2.40-2.70 (m, 2 H), 3.55-3.65 (d, J = 6.6 Hz, 1 H), 4.20-4.35 (br s, 1 H), 4.50-4.60 (m, 2 H), 4.95-5.05 (br s, 1 H), 5.65-5.80 (m, 1 H), 6.20-6.35 (dd, J = 9.8, 2.1 Hz, 1 H), 7.10-7.40 (m, 5 H); ^{13}C NMR (acetone-d_6, 400 MHz) δ 16.11 (d'), 24.89 (t'), 30.92 (q'), 34.22 (t'), 36.81 (t'), 39.38 (t'), 44.17 (d'), 49.01 (d'), 63.12 (d'), 76.64 (d'), 115.18 (t'), 126.87 (d'), 128.95 (d'), 129.30 (d'), 129.60 (d'), 135.46 (d'), 144.67 (s'), 145.90 (s'), 170.2306 (s'); exact mass m/z calcd for $C_{21}H_{26}O_3$ 326.1882, found 326.1880.

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